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# MALT SOUP EXTRACT AS AN ANTISCORBUTIC*

H. J. GERSTENBERGER, M.D.

CLEVELAND

During 1918, while studying the respiratory quotient of scorbutic infants, we decided for definite reasons to feed these infants with Keller's malt soup, a mixture containing 100 gm. of the so-called malt soup extract, which has made for itself a record of producing and never of curing scurvy. Hess,[1] for instance, reports that in his experience the malt soup preparation is the diet which has been associated with scurvy most frequently. September 6, 1918, a patient who had developed a scurvy in another institution on Keller's malt soup was given the same kind of a mixture in pursuance of the above stated aim, but on the fourth day orange juice was added to the diet, and so the surprise which we were to have later in the case of another patient was inadvertently postponed. September 26, 1918, another scorbutic patient, 11 months of age, was brought to the hospital with a history of poor development and bad stools (Table 1). He was bottle-fed since birth. From the age of 1 month on until he was 10 months old he was fed a mixture of one-half milk and one-half oatmeal water with cane sugar. Then he received for another month two-thirds milk and one-third oatmeal water. During this month he suffered from diarrhea, and as a result, the stepmother, who took charge of him at this time, frequently gave him castor oil, but without beneficial effect on the painful lower extremity. The physical examination showed a decided case of scurvy, the patient having swollen and bleeding gums about the upper and lower incisors, enlarged epiphyses, a rosary, an enlarged spleen, and increased permeability of capillaries, a swollen right knee and a very sensitive left knee. For our purposes of respiratory quotient study he was also put on Keller's soup. On the day of his admission to the hospital he received a mixture of one-half skimmed milk and one-half oatmeal, and on the following day he was offered Keller's soup, but refused most of it, taking only a total of 250 c.c. On the next day, however, he took 820 c.c. and then the full 1,000 c.c. offered him. We expected no improvement, and as we wished to see the effect of the

*From the Babies' Dispensary and Hospital and Departments of Pediatrics of Western Reserve Medical School and of Lakeside Hospital.

1. Hess, Alfred F.: Infantile Scurvy. V. A Study of Its Pathogenesis. Am. J. Dis. Child. **14**:347 (Nov.) 1917.

orange juice on the respiratory quotient and as we also wished to have the same carbohydrate intake in the preliminary period as would occur in the regular period, we gave him, besides 1,000 c.c. of Keller's soup, 60 c.c. of a 10 per cent. solution of sugar, composed of 6.5 per cent. of glucose and 3.5 per cent. of sucrose. The higher percentage of glucose was used because levulose was not available.

TABLE 1.—Analysis of Clinical History of Second Scurvy Patient

| Date, 1918 | Food | | Weight, Gm. | Temperature | | | Stools | Clinical Condition and Symptoms |
|---|---|---|---|---|---|---|---|---|
| | Kind | Amt., C.c. | | | | | | |
| Sept. 26 | Skimmed milk ½, OMW ½ | 600 | ..... | 38.1 | 37.6 | 27.6 | E | Pallor; restless; bleeding and swollen gums about incisors; right knee swollen and very sensitive, left also sensitive. Child also showed a marked rosary, enlarged spleen and epiphysis on admission; had diarrhea for a long time before admission |
| Sept. 27 | Skimmed milk ½, OMW ½ | 100 | 5,610 | 38.2 | 37.8 | 37.9 | 1 T | Same |
| | Keller's soup | 250 | | | | | | |
| Sept. 28 | Keller's soup | 820 | 5,480 | 37.0 | 37.3 | 38.0 | 3 T | No change noticed |
| Sept. 29 | Keller's soup | 1,000 | 5,550 | 37.9 | 37.6 | | 3 T | No special observation made |
| Sept. 30* | Keller's soup | 1,000 | 5,725 | 36.6 | | | 2 N | |
| Oct. 1 | Keller's soup | 1,000 | 5,855 | 36.8 | | | 1 T | Child's improved disposition noted |
| Oct. 2 | Keller's soup | 1,000 | 5,845 | 37.0 | 37.4 | | 2 N | Gums normal; joint sensitive and swelling gone |
| Oct. 3 | Keller's soup | 1,000 | 5,800 | 37.0 | 37.6 | | 5 N | Same; very happy; looks much better |
| Oct. 4 | Keller's soup | 1,000 | 5,790 | 37.2 | 37.6 | | 4 N | Same; joints negative to pressure |
| Oct. 5 | Keller's soup | 1,000 | 5,800 | 37.4 | 37.6 | | 3 N | Continued general improvement |
| Oct. 6 | Keller's soup | 1,000 | 5,800 | 37.9 | 37.9 | | 2 N | |
| Oct. 7 | Keller's soup | 825 | 5,790 | 37.0 | 37.2 | | 1 SN | |
| Oct. 8 | Keller's soup | 100 | 5,900 | 37.2 | 37.2 | | 2 T | |
| Oct. 9 | Keller's soup | 100 | 5,970 | 37.0 | 37.0 | | 1 SN | |
| Oct. 10 | Keller's soup | 100 | 5,945 | 36.8 | 37.8 | | 2 N | |
| Oct. 11 | Keller's soup | 100 | 5,900 | 37.2 | 36.2 | | 1 SN | |
| Oct. 12 | Keller's soup | 100 | 5,950 | 37.4 | 37.4 | | 2 SN | Color better |

* September 30, the patient received 60 c.c. of a 10 per cent. sucrose solution; October 1 to 7, inclusive, 90 c.c. of a solution containing 3.5 per cent sucrose and 6.5 per cent. glucose daily; October 8 and 9, 660 c.c. and October 10, 11 and 12, 90 c.c. of the same solution daily.

October 1, it was noticed that the child seemed different, but no particular attention was paid to the scorbutic symptoms, simply because we did not expect any special change. October 2, however, the child seemed so normal that an accurate inspection of the gums was made, and to our great surprise these were found to be absolutely normal. The swelling of the right knee joint had lessened, and the sensitiveness of both the left and the right knee had practically gone. With each succeeding day the child improved in general appearance and disposition, so that we could say definitely that the child had been cured of scurvy, at least of the severe, active stage of scurvy. This experience was so remarkable that nothing was said about it and observations were made to determine whether through some error the child had not

received an antiscorbutic. No evidence in this connection was discovered, however, and so it was decided to say nothing and wait for the next opportunity, which came Dec. 13, 1918.

This third patient had an enormous hematoma of the right femur, and after three days of half milk, half oatmeal water, and 2½ per cent. of cane sugar, the child was given Keller's soup, prepared with the same malt extract that had been used in the previous cases. The gums of this child were perfectly normal, and we had to depend entirely on the sensitiveness and the size of the large swelling to decide whether we had much improvement or not. After three days' observation there was no definite and positive improvement, and as the child was quite ill and had a temperature of 38.5 C., and as the respiratory quotient curves showed certain interesting features, we decided to give orange juice at this time, with the result that within a few days the child showed a distinct improvement. But the improvement was gradual, even with 90 c.c. of orange juice in twenty-four hours, so that, after all, we did not know from his experience whether or not the Keller's soup or the malt extract in the Keller's soup had also exerted any antiscorbutic influence in this child. So again we decided to wait for another opportunity, which came Dec. 30, 1918.

This fourth patient, a colored infant, 10 months of age, was brought to the hospital with a history of stomach trouble and swollen feet (Table 2). She had been artificially fed since the third week, at first for six weeks with a milk dilution, then for six months with bread and tea, and finally during the last three months with a cane sugar one-half milk and one-half water mixture. On physical examination the child showed a very marked rosary and a decided swelling of the lower extremities—especially below the knees. All the tissues about and especially above the right ankle were very much indurated, and all of these swollen areas were extremely sensitive to the slightest pressure. The child objected to moving its legs and was very unhappy and irritable. The gums showed no lesions, even though too small lower incisors had just erupted. This finding is not so very uncommon in cases of scurvy, especially as regards the lower incisors, and in no manner speaks against the correctness of the diagnosis of this case. We have had occasion to see undoubted symptoms of scurvy develop, when the gums of both the lower as well as of the upper incisors were normal. It is unquestionably true, however, that swollen, bleeding, bluish-red gums are the most dependable and characteristic sign of infantile scurvy. The epiphyses at the wrists were only slightly enlarged. After three days feeding with two-thirds milk and one-third oatmeal water, with 3 per cent. cane sugar, during which time no improvement was noticed, she was given Keller's soup made up with the same malt soup extract that had been employed for the last two cases. Ninety c.c. of artificial

orange juice were also given. The next day, January 3, the infant seemed to be passing more urine, and especially was this difference noted the following day. No attempt, however, was made to get an accurate record of the amount of urine excreted, as the patient was a little girl. After twenty-four hours of Keller's soup the child's disposition seemed to be changed for the better, and January 5 there was a marked reduction in the sensitiveness to pressure on the knees, the

TABLE 2.—ANALYSIS OF CLINICAL HISTORY OF FOURTH SCURVY PATIENT

| Date, 1918 | Food | | Weight, Gm. | Temperature | | | Stools | Clinical Condition and Symptoms |
|---|---|---|---|---|---|---|---|---|
| | Kind | Amt., C.c. | | | | | | |
| Dec. 30 | OMW ⅓, milk ⅔, cane sugar 3% | 700 | ..... | 37.3 | 37.5 | 37.1 | ... | Marked fretfulness and restlessness; pain on the slightest movement of lower extremities; decided swelling and induration of tissue above knee and especially below; marked sensitiveness to slightest touch; gums normal. Child shows a very marked rosary |
| Dec. 31 | OMW ⅓, milk ⅔, cane sugar 3% | 900 | 5,370 | 37.6 | 37.2 | 37.6 | 1 N | Same |
| Jan. 1 | OMW ⅓, milk ⅔, cane sugar 3% | 700 | 5,370 | 38.0 | 37.1 | 37.6 | 1 N | Same |
| Jan. 2* | Keller's soup | 900 | 5,175 | 36.4 | 36.6 | | 3 N | Same |
| Jan. 3 | Keller's soup | 900 | 5,145 | 36.6 | 37.2 | 36.6 | 6 SN | Disposition seems better; urinates more |
| Jan. 4 | Keller's soup | 900 | 5,130 | 36.2 | 36.5 | | 3 SN | Seems more comfortable; urination much incr. |
| Jan. 5 | Keller's soup | 900 | 5,100 | 36.6 | 37.5 | | 3 SN | Less sensitive; wet all the time |
| Jan. 6 | Keller's soup | 900 | 5,130 | 37.0 | 37.2 | | 3 SN | Swelling practically gone; sensitive only to deep pressure; happy |
| Jan. 7 | Keller's soup | 900 | 4,925 | 36.6 | 37.4 | | 2 N | Laughs and is contented; still very wet |
| Jan. 8 | Keller's soup | 900 | 4,905 | 36.5 | 36.6 | | 2 N | Legs show no swelling whatever; no pain even on deep pressure; seems entirely well |
| Jan. 9 | Keller's soup | 900 | 4,870 | 36.5 | 37.2 | | 4 N | |
| Jan. 10 | Keller's soup | 900 | 4,840 | 36.1 | 37.2 | | 2 N | |
| Jan. 11 | Keller's soup | 900 | 4,900 | 36.1 | 37.1 | | 2 N | |
| Jan. 12 | Keller's soup | 900 | 4,850 | 36.0 | 36.5 | | 2 N | |
| Jan. 13 | Keller's soup | 900 | 4,910 | 36.6 | 37.6 | | 2 N | |
| Jan. 14 | Keller's soup | 900 | 4,850 | 36.1 | 37.0 | | 3 T | |
| Jan. 15 | Keller's soup | 900 | 4,910 | 36.6 | 37.3 | | 1 N | |
| Jan. 16 | Keller's soup | 900 | 4,800 | 36.5 | 37.3 | | 1 N | |
| Jan. 17 | Keller's soup | 900 | 4,990 | 36.8 | 38.0 | 36.0 | 2 N | |
| Jan. 18 | Keller's soup | 900 | 4,990 | 36.5 | 37.5 | | 1 N | Pertussis vaccine; left knee and right ankle sensitive to pressure; is fretful. Due to effects of vaccine injection |

* From January 2 to 8, inclusive, the patient received 90 c.c. of artificial orange juice daily and from January 9 to 18, 90 c.c. of orange juice daily.

tibiae and the ankles. January 6 there was an enormous improvement, the legs being sensitive only to every deep pressure, the swelling and induration having practically disappeared. The baby moved its legs about and appeared to be all right. January 8 no swelling whatsoever could be found, and even severe pressure brought no response; the baby laughed and was very happy and contented. So that in this case we

can maintain that the child was definitely cured without receiving orange juice or any other hitherto known antiscorbutic. January 9 orange juice was given for respiratory quotient study, but no further change in the condition of the child was noticed, except on the eighteenth, when the child received an injection of pertussis vaccine and as a result developed fever and, what is interesting, a sensitiveness of the left knee and of the right ankle. This renewed sensitiveness, however, disappeared within a few days, and evidently had some direct connection with the injection of the pertussis vaccine.

TABLE 3.—Analysis of Clinical History of Fifth Scurvy Patient

| Date, 1919 | Food | | Weight, Gm. | Temperature | | | Stools | Clinical Condition and Symptoms |
|---|---|---|---|---|---|---|---|---|
| | Kind | Amt., C.c. | | | | | | |
| May 10* | S. M. A. | 250 | ..... | ..... | | | 1 SN | Pallor, fretfulness, marked swelling of right ankle and thigh; knees and ankles sensitive to slightest touch; suppurating hematoma in right buttock. Râles at both bases |
| May 11 | S. M. A. | 490 | 7,170 | 39.7 | 38.8 | 39.6 | 2 SN | Same |
| May 12 | S. M. A. | 390 | 7,340 | 40.2 | 38.0 | 39.0 | 3 SN | General condition decidedly better; no local change |
| May 13 | S. M. A. | 690 | 7,260 | 37.7 | 39.4 | 38.4 | 2 SN | Much improved generally; looks about |
| May 14 | S. M. A. | 790 | 7,220 | 39.0 | 38.5 | 37.5 | 3 SN | Marked increase in urination; even more comfortable. Still breaths rapidly, looks "pneumonic" |
| May 15 | S. M. A. | 970 | 7,430 | 39.4 | 38.8 | 39.2 | 3 SN | Marked increase in urination; swelling of right ankle gone entirely; legs can be moved with little discomfort; tries to smile. Pseudolabor pneumonia at left base |
| May 16 | S. M. A. | 960 | 7,210 | 38.3 | 39.4 | 37.7 | 5 T | Right ankle also much reduced; sensitiveness of joints practically gone; smiles. While scorbutic symptoms have markedly improved, pneumonic picture remains unchanged |
| May 17 | S. M. A. | 970 | 7,290 | 39.5 | 38.4 | 38.6 | 5 T | Child moves legs about of own accord without pain; no tenderness except in right hematoma area |
| May 18 | S. M. A. | 900 | 7,330 | 38.4 | 39.5 | 38.0 | 3 T | Is interested and can smile |
| May 19 | S. M. A. | 905 | 7,620 | 39.5 | 39.5 | 38.0 | 3 T | |
| May 20 | S. M. A. | 960 | 7,550 | 37.0 | 37.6 | 38.2 | 3 T | Pneumonia picture changed |
| May 21 | S. M. A. | 950 | 7,340 | 37.4 | 37.4 | 36.8 | 5 SN | Pneumonia picture gone |
| May 22 | S. M. A. | 1,000 | 7,320 | 36.9 | 37.0 | 37.1 | 1 N | |
| May 23 | S. M. A. | 990 | 7,330 | 37.0 | 36.8 | 36.4 | 4 SN | Right thigh still slightly tender; healing of suppurative hematoma. Looks fine; seems very well; few räles still present at left base |
| May 24 | S. M. A. | 985 | 7,340 | 36.6 | 37.2 | 37.5 | 6 SN | |
| May 25 | S. M. A. | 985 | 7,295 | 36.8 | 36.9 | 37.5 | 5 SN | |
| May 26 | S. M. A. | 885 | 7,295 | 36.8 | 37.4 | 37.7 | 8 SN | |

* May 10, the patient received 60 gm. of malt soup extract, and from that day on, 100 gm. daily.

May 10, 1919, a fifth baby, 8 months old, was brought to Lakeside Hospital with a diagnoss of osteomyelitis (Table 3). The mother stated that the child had been coughing for two weeks, and had also developed at about that time a large swelling on the right buttock, which was opened by a physician. While this wound had drained quite

well, the tumor below the abscess seemed to get larger and more tender. The patient was admitted on the surgical service and then taken over to the pediatric service with a diagnosis of scurvy. The right thigh between the knee and hip was markedly swollen and the old incision was still oozing slightly. Both knees and the right ankle were especially sensitive, also the left ankle, but not as much as the other three joints. Around and especially above the right ankle there was marked and hard induration, and through the skin bluish areas could be seen. The child was pale, had a marked rosary of the "necropsy chest" type, enlarged epiphyses at the wrists, was very fretful, laid in a frog fashion, and would cry severely as soon as its lower extremities were moved.

Instead of giving this child Keller's soup we gave it S. M. A. (synthetic milk adapted) in order to exclude the possible therapeutic effect of the one-third certified milk that had been used in the Keller's soup for the other children recorded above. A large batch of 20 quarts of S. M. A. was made at one time and prepared over the regular route of pasteurization. We offered the child 1,000 c.c. of S. M. A., but inasmuch as its appetite was very poor we had to resort to gavage after a few days. The antiscorbutic value of S. M. A. is small, and not adequate to prevent a normal child that is getting nothing but S. M. A. from developng scurvy, so that any therapeutic effect obtained by the giving of S. M. A. could not be explained by its administration. Therefore, in this case we gave the malt soup extract, a part of the same lot that had been used for the preparation of the other Keller's soup mixture used in the previously described cases, in the same amount in which it had been administered in the form of Keller's soup, namely, 100 gm. for each twenty-four hours. May 11, the child received 60 gm.; May 12, 100 gm., and after that 100 gm. daily were given of the malt soup extract in addition to the 1,000 c.c. of S. M. A. At first the malt soup extract was given separately, later on it was mixed with the S. M. A., just before it was offered to the child, and so it was not exposed to a temperature above 37 C. The subjection of this malt soup extract to a higher temperature would have made no difference, however, because it was exposed to boiling temperature in all of the previous cases, and in all but the last to an additional temperature above 100 C., but it still retained sufficient antiscorbutic value to cure, without question, the second and fourth infants.

When this patient was first admitted it showed besides the lesions already described, râles at both bases, especially on the left side, accompanied with a temperature that varied daily anywhere from 37.8 to 40.1 C. May 15 there was a definite and marked impairment of resonance of the left lower lobe, accompanied by bronchial breathing so that we could make a diagnosis of pseudolobar pneumonia. As a result of

this pneumonia, the infant did not make a complete change for the better until May 20. The presence of the pneumonia, however, did not obscure the definite and marked improvement in the scorbutic symptoms after the beginning of the malt soup therapy.

As stated above, May 11 the child received its first malt soup extract, and May 13 there could be seen a marked improvement in the joint sensitiveness. As a matter of fact, some improvement was noted May 12, twenty-four hours after the beginning of the therapy. May 14 a marked increase in urinary excretion was also noted, but inasmuch as the fluid intake was low, owing to the poor appetite of the child and its resistance to gavage, the increased urination may have been due more to the increased intake rather than to any diuretic effect of the malt soup extract, although, in all probability, the latter was a factor when one considers that the other children did take more fluid before they received their malt soup extract in the form of Keller's soup and, nevertheless, showed a marked increase in urinary excretion. May 15 the brawny induration of the right ankle was entirely gone, the tenderness of the left knee was markedly diminished, and the child offered no complaint when the left knee and thigh were flexed on the abdomen. Only the right thigh, owing to the presence of the suppurating hematoma, was still protected by the infant against too marked a movement, but even this swelling of the right thigh had been reduced in size, and there was also a decided improvement in the general condition of the child. It became interested in things, and, even though it was still very sick with its pneumonia, it tried to smile and would watch objects that were placed before it, something which it had not done before.

On the next day, May 16, the right thigh had reduced in size enormously and the baby was much more improved, as far as its general disposition was concerned; it smiled and the knees could be flexed without causing any pain. The same was true of the ankles. The pneumonia was still causing a rise of temperature up to 39.5 C., giving beautiful proof that the improvement was due to something different than a change in the condition of the lungs, which clinically could not be recognized. To our great surprise and amazement it was learned from the history that this infant had received nothing but its mother's breast-milk. No oranges, tomatoes, potatoes or any other foodstuffs were given it. The mother herself was well, had had no bleeding gums, no painful extremities, and had been eating a general diet, including potatoes. This child was the result of the sixth pregnancy, the first two having ended at six months, while the third, fourth, and fifth went to full term and brought forth infants who are living and well.

We appreciate fully that this history raises a justified doubt as to whether the symptoms in this child were due to scurvy. And yet, after considering the physical findings and the type and course of improvement in the picture after the giving of the malt soup extract, on the one hand, and, on the other, the great improbability that under the same treatment such a marked and rapid change in the condition of the extremities could have occurred if the lesions were due solely to some sort of an infection—we cannot come to any other conclusion than that this case is one of the rare cases of scurvy in breast-fed infants. Possibly when the etiology and the pathogenesis of scurvy will have been clearly established cases such as this one will appear less enigmatic.

So this last patient is also put down as a severe case of scurvy cured in its acute stage by the administration of malt soup extract in a dose of 100 gm. per twenty-four hours, making a total of at least three cases of severe and unquestionable scurvy, cured by the administration of malt soup extract.[2]

As stated before, Keller's malt soup is a food that is very prone to cause scurvy in infants, and yet there can be no question as to its curative effect in three of the above described cases, an effect that can be dissociated in these severe and yet rapidly cured cases from the quantity of the milk, the heating factor and the ageing factor, as all of these detrimental factors existed in each of the three cases of cure, as the following data will show:

The only factor, besides the malt soup extract itself, that might be considered as having been responsible for the improvement is the quality of the milk, for certified milk was used in the preparation of each batch of food, and it might be imagined that cows producing certified milk are possibly given a diet that would put into the milk more anti-scorbutic substances than would be found in the milk of the ordinary milk cows, which most likely has been used, as a rule, in the making of Keller's soup.

However, neither the fact that certified milk was used, nor the possibility of a greater anti-scorbutic content of such a milk make this idea seem at all probable, as the certified milk used in making the curative Keller's soup for infants came from the same certified dairy from which is obtained the certified skimmed milk which is used in the manufacture of S. M. A. milk, a food which will cause scurvy, even though it contains the same amount of milk as Keller's soup, if no anti-scorbutic is given in addition. And, finally, the food which the cows at the certified farm received was dry and varied in its source, as one would

2. The malt soup extract used in this work was labeled 8149 by the Borcherdt Company.

have expected from the fact that the one infant was fed from Sept. 27 to Oct. 12, 1918; the other from Jan. 2 to Jan. 18, 1919; and the third from May 10 to May 26, 1919. So it would be a strange coincidence indeed that cows fed at such widely separate periods on dry food-stuffs, known to have come from different sources, should produce a milk of such high antiscorbutic power that even in the quantity of not more than 330 c.c. for twenty-four hours, boiled, pasteurized, or even sterilized under pressure, and from two to three weeks old, would produce results so paradox to the universal proscorbutic experience with Keller's soup. Therefore, it would seem much more rational to assume that the one and the same batch of malt soup extract which was used in the case of each of these infants was, in all probability, responsible for the good therapeutic results.

The second infant received Keller's soup which was made with certified milk in the ordinary way by boiling, and which then, in addition, was sterilized under pressure for thirty minutes. The entire batch consisted of thirty-two quarts, and for seventeen consecutive days the patient received exactly the same food, making the last quart eighteen days old.

It may be interesting to note in this connection that the remainder of this lot of Keller's soup which cured this infant of its scurvy, produced a fatal scurvy in a number of guinea-pigs, even though their stools were normal during the earlier half of the experiment and decidedly diarrheic during the latter half, and even though they ate more than enough to meet their caloric and fluid requirements. At the necropsy most of these pigs had their large intestines one-half to two-thirds full of a soft, thin stool.

The fourth infant received Keller's soup, all of which was also made at one time, and the last quart of which was fourteen days old when consumed. This batch of food, however, was not subjected to sterilization under pressure.

Evidently, all of these factors were not adequate to reduce the curative properties of the malt soup extract to a level below immediate and marked therapeutic efficacy.

No conclusive facts regarding the cause of the presence of the antiscorbutic properties of malt soup extract No. 8149 can be given at this time. In the light of our present knowledge, however, there can be only one explanation, as a visit to the factory and a conference with the manufacturer of the malt soup extract convinced me that lot 8149 was alkalinized in the prescribed manner with methyl red as the indicator.

The most probable explanation would seem to us to be that the barley from which the malt used for the manufacture of the malt

soup extract was derived, had reached an age and stage of germination at which much antiscorbutic substance was produced, or that the barley grain itself possessed an unusually high amount of potential antiscorbutic material.

Valentin Fürst[3] called attention to the fact that while plain barley, oats, peas, etc., have none or not sufficient antiscorbutic powers to prevent the development of scurvy in guinea-pigs, the very same barley, oats, peas, etc., when brought to germination by being kept in a moist warm room for about three days, develop marked and adequate antiscorbutic properties, as tested out on guinea-pigs, and recently in the Chemical Abstracts (April 10, 1919) H. S. Paine[4] reports that E. Weill, G. Mouriquard and Mlle. Peronnet have found that cereal grains of ten days germination age have a greater antiscorbutic value than those of three days old.

If this is the true explanation of the presence of the antiscorbutic factor in the malt soup extract, then it should be possible to use in the manufacture of malt soup extract only malt that has been made from barley of the proper age and state of germination. This would be an addition to our present list of antiscorbutics of another agent of real value as malt soup extract can be used to advantage in other respects in the diets of infants and young children, especially of those that are inclined to be constipated.

The difference in therapeutic results between infants, on the one hand, and guinea-pigs, on the other hand, is undoubtedly due to the decidedly larger antiscorbutic requirements of the guinea-pigs.[5] From the work of Chick, Hume, Skelton [6] we know that a guinea-pig of about 250 gm. weight requires from 80 to 100 c.c. of raw milk daily to prevent the development of scurvy or, at least, to postpone its appearance for a long time, and according to Hess [7] the infant requires about 500 c.c. of raw milk in twenty-four hours. Such infants will weigh on an average at least 5,000 gm.; in other words, twenty times as much as a guinea-pig, and yet infants require only five times as much milk as do guinea-pigs to protect them against the development of scurvy.

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3. Fürst, Valentin: Weitere Beiträge zur Aetiologie des experimentellen Skorbuts des Meerschweinchens, Ztschr. Hyg. u. Infekt. Krankh. **72**:132, 1912.

4. Paine, H. S.: Chemical Abstracts **13**:749 (April 10) 1919. Appearance of an Antiscorbutic Substance During Germination of Cereals. E. Weill, G. Mouriquard, and Mlle. Peronnet, Compt. rend. soc. biol. **81**:607, 1918.

5. Chick, H., Hume, H., and Skelton, R.: Antiscorbutic Principles in Limes and Lemons, Lancet **2**:735 (Nov. 30) 1918 .

6. Chick, H., Hume, H., and Skelton, R.: Antiscorbutic Value of Milk in Infant Feeding, Lancet **1**:1 (Jan. 5) 1918.

7. Hess, A. F., and Unger, L. J.: Factors Affecting the Antiscorbutic Value of Foods, Am J. Dis Child. **17**:239 (April) 1919.

This experience with the guinea-pigs and infants fed with the same Keller's soup would indicate that the antiscorbutic content of the malt soup extract was relatively not as great as that of orange juice or tomato juice, although it was evidently sufficient to cure severe acute cases of scurvy in infants, and it may well be possible that a malt soup extract could be manufactured whose antiscorbutic powers would be distinctly greater than those present in the lots used for this work.[8]

## CONCLUSIONS

1. A report is made of a rapid and marked cure, such as is experienced with orange juice, of three cases of severe infantile scurvy by the administration of 100 gm. of malt soup extract. In two of these the malt soup extract was given in the form of Keller's soup, in the third, in conjunction with S. M. A.

2. The explanation offered for the presence of the antiscorbutic property in this No. 8,149 lot of malt soup extract is that it was, in all

8. Since this article was submitted, the remainder of lot 8,149 was given to three infants, two of whom had clear-cut cases of scurvy, while the other never got beyond what at most could be called a subacute form. The data obtained were inconclusive and consequently are of no value. In the last mentioned child, seen during September, 1919, an otitis media, a pyelitis and a probable enteritis follicularis were responsible for the poor condition and the lack of improvement. The malt soup extract was given mainly together with S. M. A., but for five days it received it in the form of Keller's soup made with certified milk which came from the same farm that produced the milk used in the feedings for the cured cases presented in the article.

The first child had a clear-cut scurvy and came to the hospital during a severe hot spell in July, 1919, suffering in addition from a severe dyspepsia. The vomiting greatly limited the amount of malt soup extract retained and as signs of dehydration appeared the observation had to be stopped and the diet replaced by large doses of orange juice, barley water ad libidum and saline infusions with beneficial results.

The other child, 7 months old and weighing 7,000 gm., was seen in November, 1919, ill with a definite scurvy. It received the very last part of lot 8,149, which was just enough for four days. No definite improvement was registered at the end of this time. It was then given for four days 100 gm. of lot 9,322, neutralized with potassium carbonate, which had recently been made at the factory. This also was without beneficial result and so for the next five days 100 gm. of lot 9,322, to which, however, no potassium carbonate had been added at the factory, were administered, but again no betterment was observed. Thirty c.c. of orange juice were given four times per day and this brought good results. The symptoms, however, did not disappear as completely and as quickly as usual. It is possible that this child required an especially large amount of antiscorbutic to remain well, as the mother, who is intelligent and who seems dependable, states emphatically that the child got 1 teaspoonful of orange juice daily from his third month on and "did not need any more, because his bowels were all right." This child was fed since its second month on a simple dilution mixture at one of the local infant welfare stations.

probability, made from barley of the proper age and state of germination or from a lot of barley possessing an unusually high amount of potential antiscorbutic material.

3. The suggestion is made that all malt soup extract could be manufactured from barley of an age and state of germination that would insure its large and adequate content of the antiscorbutic factor, and that in this manner another antiscorbutic, of value also in other respects to infants and children, could be added to the list of our regular and dependable antiscorbutics.

# ANEURYSMS OF THE THORACIC AORTA IN CHILDREN

## WITH REPORT OF TWO CASES *

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Aneurysm of the thoracic aorta is a rare condition in children. I have been able to collect and review thirty-one cases from the literature, besides the two cases which I have to report.

### ETIOLOGY

There is a great diversity of opinion on this subject, mainly because the real causative factors have not been worked out in many cases. Some authors believe that syphilis is practically always the prime factor in children as in adults, but a careful study of the available cases does not confirm this view. Bronson [1] has grouped these cases according to the etiologic factors into: (1) those aneurysms due to atheromatous degeneration; (2) those resulting from trauma (rare); (3) those due to erosion of the aorta from without; (4) a few following congenital malformations, and (5) last, but probably the most important factor in childhood, aortic aneurysms following in the wake of acute infectious diseases. Osler remarks that in adults the specific fevers commonly cause areas of degeneration in the intima of the aorta and occasionally in the media. Klotz [2] has shown that in childhood the aorta may be attacked during an acute infectious disease, especially those due to the streptococci. He claims that the organisms gain entrance to the aortic wall through the vaso vasorum and lodge in the media, causing degenerative changes which lead to a gradual weakening of the wall, with resulting dilatation, fibrosis and possibly aneurysm.

A summary follows of the cases in which the apparent determining cause was an acute infectious aortitis.

### CASES DUE TO ACUTE INFECTIOUS AORTITIS

CASE 1.—A definite history of five severe attacks of chorea was given. During the third attack the heart was involved. This attack was followed by diphtheria. During the fifth attack the aneurysm was diagnosed, five years

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* Inaugural Address before the Chicago Pediatric Society.

1. Bronson and Sutherland: Ruptured Aortic Aneurysms in Childhood, with Report of a Case, Brit. J. Child. Dis. **15**:16, 1918.

2. Klotz, O.: Arterial Lesions Associated with Rheumatic Fever, J. Path. & Bacteriol. **18**:259, 1913.

after the initial chorea. The blood Wassermann was negative. There were no signs of congenital syphilis, nor any family history of syphilis. Three other children, one older and two younger, were well.

CASE 2.—This patient developed symptoms of "heart trouble" after an operation for appendicitis, with a postoperative pneumonia, which in turn was followed by arthritis. Two weeks after this acute arthritis, palpitation of the heart began, confining him to bed for six months. He had had nine previous attacks of acute arthritis which lasted for a week at a time. Two negative blood Wassermanns were obtained; one at Michael Reese Hospital and the other at Cook County Hospital, the interval between the tests being five months. No signs of congenital syphilis were present. The mother and father both died of pneumonia. One sister died from an unknown cause.

## REVIEW OF LITERATURE

MacNalty [3] reports that his patient had scarlet fever at the age of 4 years, measles at 5 and pharyngitis and cough at 8, followed by heart symptoms which persisted off and on. The aneurysm was diagnosed six years after the onset of the heart symptoms. The child had a cleft palate and hare lip, but no signs of syphilis. There was no family history of syphilis, although the father had heart disease.

Klotz [2] reports that his patient had arthritis six months before, following which heart symptoms developed and "heart disease" was diagnosed. Then shortly before death he developed another acute arthritis and endocarditis. Positive blood cultures of pure streptococci were obtained. Sections through the aneurysm at necropsy revealed acute inflammation, and streptococci were found in these tissues. No evidence of syphilis was revealed.

Roy [3a] believes his case was caused by an acute infection of some kind, but admits that the cause is unknown. There was no history nor evidence of syphilis.

Jordan [4] reports a history of rheumatism with possible septic aortitis in his case. No history nor evidence of syphilis was revealed.

Thieberge's [5] patient had an acute endocarditis four months before the aneurysm was diagnosed. The family history was negative. There were no evidences of syphilis.

A. A. Smith's [6] patient had acute arthritis one year before the aneurysm was diagnosed.

Bacelli's [7] patient had two attacks of acute articular rheumatism. One was two years before, and the other six months before the aneurysm was diagnosed. There was no clinical evidence of syphilis. The family history was negative.

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3. MacNalty, A. S.: Proc. Roy. Med. Soc., London **10**:35 (Clin. Sec.) 1909.
3a. Moizard and Roy: Ann. de méd. et chir. inf. **12**:149, 1908.
4. Jordan, A. C.: Lancet **1**:515, 1903.
5. Thibierge: La France méd. **2**:913, 1881.
6. Smith, A. A.: Med. Rec. **44**:349, 1893.
7. Bacelli, G.: Semaine méd. **18**:137, 1898.

Le Boutillier's [8] patient gave a history of two attacks of pertussis, the first when 9 days old, the other at the age of 3 years, and arthritis at 4 years, at which time some heart trouble was diagnosed. Typhoid developed at 7 and measles at 9. The aneurysm was diagnosed at 9. No physical evidence of syphilis was present. One child died of pertussis. Otherwise, the family history was negative.

### CASES DUE TO SYPHILIS

A summary of the cases in which the apparent determining cause was syphilis is interesting.

Heiman [9] reports the case of a woman and her boy who had a four plus blood Wassermann reaction. The mother had had two miscarriages and the father died of epilepsy. The child had several attacks of acute articular rheumatism, the last one about two years before the aneurysm was diagnosed. The child had an enormous spleen and a tumor of the liver which was assumed to be a gumma.

Willson [10] reports a case in which the father had a chancre, saddle nose and developed epilepsy at 21. The mother was healthy and showed no evidence nor history of syphilis. A congenital heart lesion was diagnosed in the child at 6 weeks of age and the aneurysm was found at 4 years.

A study of the aortas of still-born infants often reveals mononuclear infiltration about the vessels of the media, spirochaetes and early degenerative changes. Thus, we can easily realize how such changes may give rise to aneurysms later in life in congenital syphilitics.

### CASES DUE TO TRAUMA

Cases apparently due to trauma are rare.

In McKeen's case [11] the symptoms followed severe trauma to the chest six months before the aneurysm was diagnosed. Pendin [12] also believed that his case followed a trauma.

### CASES DUE TO EROSION

A summary of those cases apparently due to erosion from without follows:

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8. Le Boutillier, T.: Case of Aneurysm of Transverse Portion of Aortic Arch, with a Table of Reported Cases Under Twenty Years of Age, Am. J. M. Sc. **125**:778, 1903.

9. Heiman, H.: Aneurysm of Ascending Arch of Aorta in a Boy of Thirteen, Arch. Pediat. **36**:543 (Oct.) 1919.

10. Willson, R., and Marcy, A.: Proc. Path. Soc. Phila. **16**:63, 1914.

11. MacKeen, R. A. H.: Med. News **61**:272, 1892.

12. Pendin, A.: Ein Fall von Aneurysm Aortae Ascendenti bei einem 12 jährigen Mädschen, St. Petersburg med. Wchnschr. **7**:195, 1890.

Hutchinson [13] reports that in his case the aorta was healthy to the edges of the aneurysm, which appeared to be a caseous gland ruptured into aorta.

In Smith and Targett's [14] case the posterior mediastinum was matted together with inflammatory products, and the aorta had been eroded from without.

Willett [15] showed that in his case the aneurysm was due to the discharge of a suppurating lymph gland into the aorta.

Jackson Clarke described two cases in which aneurysm was due to ruptured caseous lymph glands.

### CASES DUE TO CONGENITAL MALFORMATION OF AORTA

A number of authentic cases have been recorded of a thoracic aortic aneurysm resulting from congenital malformation of the aorta.

Bronson and Sutherland [1] report a case in which the aorta was stenosed in the ascending portion, proximal to which was an aneurysm. There was no history or evidence of syphilis; the Wasserman was negative; no spirochetes nor aortitis were found. There had been no acute illnesses. The family history was negative.

In Wasajerna's case a nearly complete congenital stricture was present in the ascending aorta with an aneurysm just proximal to it.

In Smith and Targett's case the aneurysm was distal to a congenital stenosis.

In Armitage's case a congenital heart lesion was present. The aneurysm was diagnosed at 7 years of age.

The symptoms of two cases appeared suddenly following an acute exertion. In these cases aneurysm had not been diagnosed until the appearance of the acute terminal symptoms.

### PREDISPOSING CAUSES

*Age.*—Twenty-one cases occurred under 12 years, and twelve cases between 12 and 18 years. At 2, one case occurred; at 3, one case; at 4, five cases; at 5, three cases; at 6, two cases; at 7, one case; at 9, four cases; at 10, one case; at 11, one case; at 12, three cases; at 13, three cases; at 14, two cases; at 15, three cases; at 16, one case; at 17, two cases; at 18, two cases.

*Sex.*—Twenty patients were boys, and ten were girls.

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13. Hutchinson: Tr. Path. Soc. London **5**:104, 1854.
14. Smith, F. J.: Aneurysm of Aorta in a Boy of Nine Years, Tr. Path. Soc. Lond. **48**:53, 1897.
15. Willett, E.: Aneurysm of Aorta in Child of Four Years, Tr. Path. Soc. Lond. **43**:38, 1892.
16. Wasajerna, E.: Ein Fall von Aortaruptur nach Schlittschuhlaufen, Ztschr. f. klin. med. **90**:405, 1903.

PATHOLOGY

*Heart.*—The heart was normal in nine cases. It was hypertrophied in ten cases, in all but two of which valvular lesions were present. The aortic valve was diseased in twelve cases. The mitral valve was diseased in eight cases. The tricuspid valve was involved in one case.

Thus, as far as the heart was concerned, hypertrophy alone was present in two cases; hypertrophy with only the aortic valve involved was present in two cases; hypertrophy with both the aortic and mitral valve involved was present in six cases; hypertrophy with only the mitral involved was present in one case; aortic and mitral involvement without mention of hypertrophy was present in one case; and aortic valve involvement without mention of hypertrophy was present in four cases.

*Aorta Apart from the Aneurysm.*—In seven cases the aorta was normal; in six cases atheroma was found; in two cases there was an acute septic aortitis, and in three cases stenosis of the aorta near the aneurysm was present.

*Pathology of the Aneurysm.*—The aneurysm was located in the ascending arch in twenty cases; in the descending arch in two cases, and in the transverse arch in five cases.

*Sac.*—The description of the sac is mentioned in relatively few of the cases.

In Willett's case [15] the opening was irregular and small and the walls in places were as thick as the aorta. Microscopically, it appeared like an old blood clot with an attempt at a lining membrane. He considered that it might have been a ductus arteriosus remaining open at its distal end, or the remains of a large lymph gland with its contents discharged into the aorta. The heart was normal.

In R. T. Smith's case,[17] an aneurysm the size of a walnut had ruptured into the pericardium. The heart showed mitral disease and the aorta showed atheroma.

In Hutchinson's case,[13] the aneurysm was the size of two chestnuts. The heart and vessels were normal.

In Sanne's case,[18] the sac was the size of a small nut. The heart showed aortic valve involvement, and the aorta showed atheromas.

In Bronson and Sutherland's case [1] a fusiform aneurysm the size of the heart was present in the ascending arch. The walls were 3 mm. thick. All the valves were normal, as was the myocardium, although the left ventricle was hypertrophied. The aorta was stenosed between the ductus arteriosus and the left subclavian artery. Microscopically, the thickening of the walls was due to hyalin sclerosis affecting the

17. Smith, R. T.: Lancet **1**:626, 1834.
18. Sanné: Rev. méns. d. mal. de l'enf. **5**:56, 1887.

deep intima and underlying media. The cells were few and of the connective tissue type. No bacteria, or spirochetes or evidences of aortitis were found.

In Klotz's case [2] a saccular aneurysm the size of a pigeon's egg was located in the ascending aorta. The heart was hypertrophied, the mitral and aortic vales were involved and a septic aortitis was present. Infarcts were present in various organs. Microscopically, the tissues of the heart valves and ascending aorta were infiltrated with polymorphonuclears and other evidences of acute inflammation. Streptococci were found in these tissues and in the blood.

The roentgen-ray is of great aid in determining gross pathologic features during life, but has only been used in Bronson's, Heiman's and my own cases as far as can be ascertained. The electrocardiograph also is of marked help in determining the condition of the heart during life. It was employed in Heiman's and in my cases.

## SYMPTOMS

Many of the symptoms were those due to the accompanying heart lesion with decompensation.

*Symptoms.*—In those cases in which symptoms referable to the aneurysm are mentioned, the onset was sudden in five cases (during exertion) and gradual in the rest. Dyspnea was present in twelve cases. Cough was present in seven cases, although no particular variety was described. Precordial pain was present in six cases and palpitation in five.

*Physical Findings.*—Only the physical findings referable to the aneurysm are noted. A systolic murmur, loud and hårsh over the base and transmitted up into the vessels, was present in nineteen cases. This was accompanied by a softer diastolic murmur when aortic regurgitation was also present. Increased dullness over the aortic arch area was present in thirteen cases. A systolic thrill over the base and great vessel area occurred in ten cases. Expansile pulsation of an abnormal tumor in the neck (suprasternal fossa) occurred in eight cases. One radial pulse was slowed in five cases and a tracheal tug was noted in one case.

The blood pressure in the four cases in which it was noted was 170 mm. of Hg, 140 (syphilitic case), 135 and 125, respectively.

The electrocardiograph in Heiman's case showed a left ventricular predominance, the notching of R in Lead II and the inversion of T in all three leads. In my case, the findings are noted in the report of the case.

*Duration.*—The duration from the beginning of symptoms was from three days to eight years. In those cases where the duration was

noted it was as follows: three days, ten days (2 cases), two months, three months, six months (3 cases), two years, three years, four years (2 cases), six years, seven years and eight years, respectively.

*Causes of Death.*—The causes of death were: Rupture into the pericardium, eight cases; acute endocarditis, three cases; acute pericarditis, two cases; asphyxia, two cases; cardiac decompensation, two cases; pneumonia, two cases; smallpox, one case; tuberculous meningitis, one case.

## REPORT OF CASES

CASE 1.—*History.*—R. M., a schoolboy, aged 11, entered the Cook County Hospital, June 17, 1919. Three years previously, four weeks after surviving an appendectomy and postoperative pneumonia, the patient developed polyarthritis. Two weeks later, heart symptoms developed which confined him to bed for six months, after which he was able to do light work. Pain in the precordium was present for the nine months preceding his entrance to the hospital. This pain was continuous, with severe exacerbations, causing him to cry, lie down and grit his teeth. At other times, the pain was of a dull aching character and did not keep him awake at night. It was located in the precordium, especially to the left of the midline, but did not radiate. For the previous month, he had pains and itching in the palms and soles. Dyspnea was present on exertion, but was not marked. Otherwise the boy was in good shape, felt well and had no other symptoms.

His previous illnesses, besides those immediately antedating his "heart trouble," were nine previous attacks of acute arthritis, usually involving the knees and confining him to bed for about one week at a time. No such attack had been present for the past three years. He developed influenza in the fall of 1918, but was in bed only five days. The patient had chickenpox and pertussis when very young.

*Family History.*—The father was a soldier and died of pneumonia nine years ago. The mother died of influenza in 1918. One sister died of unknown cause. No heart disease existed in the family.

*Physical Examination.*—Patient was a well nourished boy, about 11 years old, not acutely ill, and walked into the hospital. The pupils were equal and regular, reacting well to light and accommodation. The tonsils were hypertrophic, but contained no pus nor caseous plugs and were not reddened. Two carious teeth were present but no root abscesses.

The radial pulse was equal on both sides, 100 per minute when sitting at rest, regular and distinctly of a very forcible water-hammer type. A capillary pulse was present (seen on lips and fingernail beds). The large peripheral arteries pulsated visibly and forcibly, i. e., the carotids, brachials and dorsal pedals. A pistol shot tone could be heard over the femoral artery with a to and fro murmur.

CHEST: *Inspection* of the chest revealed a regular easy type of respiration, 24 per minute while sitting at rest. The chest was symmetrical and normally formed; no bulging was present and both sides were equal at the nipple line. The circumference at this level was 28 inches at rest, 29 inches during inspiration and 27.5 inches after expiration. A diffuse heaving pulsation was present over the precordium, especially localized at the apex in the sixth interspace at the midaxillary line. A violent throbbing was present in the suprasternal region and carotids.

*Palpation* confirmed the above findings. A systolic thrill was felt over the aortic area, becoming more pronounced toward the neck. No thrill was present over the apex. *A dome-shaped semiglobular mass was felt projecting upward from the suprasternal notch,* more to the right than to the left. This mass

had a violent expansile pulsation with a marked thrill and bruit. The mass measured 7.5 cm. wide, extended 4 cm. up into the neck at the height of pulsation and 3 cm. at the rebound. Its pulsation was synchronous with that of the heart. A tracheal tug was present.

*Percussion* revealed the following areas of dulness: At the first interspace, 4 cm. to the right and 4 cm. to the left of the midsternal line; at the second interspace: 4 cm. to the right and 5 cm. to the left of the midsternal line; at the nipple level: 4.5 cm. to the right and 12 cm. to the left of the midsternal line. The greatest transverse diameter is at the sixth interspace, 7 cm. below the nipple line: 4 cm. to the right and 14 cm. to the left of the midsternal line. The greatest oblique diameter is from the second rib to the sixth interspace, and measures 21 cm.

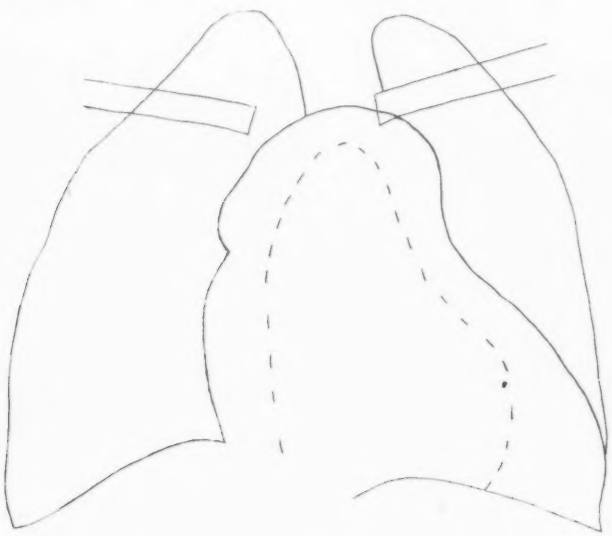


Fig. 1.—Case 1. Orthodiagram of heart, aortic arch and lungs, showing the aneurysmal dilatation of ascending portion and arch of aorta, and the enlarged heart. ------ represents the outline of about the normal sized heart and aortic arch in a child of this weight and age. Orthodiagram made by Dr. E. Blaine during fluoroscopic examination.

*Auscultation* reveals a loud, harsh, rasping to-and-fro systolic-diastolic murmur, heard all along the sternum, best to the left of the sternum over the third costochondral junction, and transmitted up toward the bulging in the neck where it is mainly systolic (very loud and rough), and down toward the apex it diminishes rapidly in intensity. About half way toward the apex there begins a presystolic-systolic murmur, which becomes quite loud at the apex, but not as loud, however, as the first murmur is over the aortic area.

ABDOMEN: The abdomen is negative, except for tenderness of the appendix scar; and the liver is palpable one and one-half fingers below the costal margin. Marked epigastric pulsation, synchronous with the heart beat, is seen.

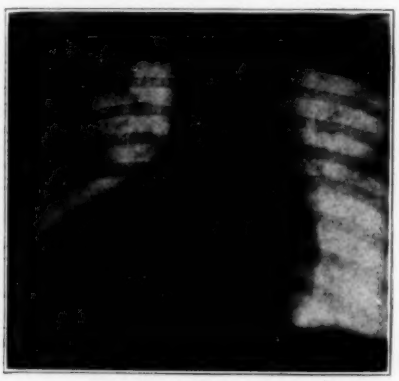
The finger nails are slightly cyanotic, and slight clubbing of the fingers is present. The reflexes are normal

*Blood Pressure.*—The blood pressure readings were as follows: June 19: Right arm, systolic 140, diastolic 30; pulse pressure, 110. Left arm, systolic 135,

diastolic 25; pulse pressure, 110. June 30: Right arm, systolic 132, diastolic 10. Left arm, systolic 120, diastolic 10.

*Laboratory Examinations.*—The blood Wassermann was negative at two reliable hospital laboratories on two successive occasions at an interval of six months. The lipoid, cholesterinized and straight Wassermann tests were all negative. The urine was repeatedly negative. The blood picture showed 4,800,000 erythrocytes, 80 per cent. hemoglobin, 14,000 leukocytes, of which 15 per cent. were small mononuclears, 5 per cent. large mononuclears, 78 per cent. polymorphonuclear neutrophils, and 2 per cent. eosinophils.

*Course.*—At first, the patient complained greatly of precordial pain and burning sensations in the hands and feet. The temperature was 98.2 F.; pulse 96, and respiration, 20. Rest in bed and moderate doses of digitalis were administered. By the end of fifteen days these symptoms had gradually diminished and disappeared. At that time the patient felt very comfortable. Temperature, 98 F.; pulse, 100; respiration, 22. He was then allowed up in a



Figs. 2 and 3.—Roentgenograms, anterior and posterior view. The heart is of the aortic valve lesion type with a large left ventricle and increased right auricle. The aortic shadow is very greatly increased, and this shadow increase extends into the base of the neck. This condition is an aneurysmal dilatation of the ascending portion and arch of the aorta.

wheel chair. A month after admittance, he was up and about and the digitalis was discontinued. The patient has been feeling well since.

CASE 2.—*History.*—G. H., a Jewish school girl, aged 9, entered Michael Reese Hospital, March 15, 1908. She had been in good health until 4 years of age, when she developed chorea, which was very severe, lasting six weeks. Her heart was not affected. She remained well for eight months and then developed a second attack of chorea, lasting six weeks, not as severe as the first, and not involving the heart. Nine months later, a third attack of chorea developed, complicated by diphtheria. Her heart was "weak" at this time. Ten months later a fourth mild chorea occurred, lasting three weeks and definitely affecting her heart (according to physician in attendance at that time). She remained well for eighteen months, and then the attack began which brought her to the hospital. The worst of the condition was over after two weeks in bed at home. The patient walked to the hospital and had a typical chorea minor. Dyspnea on exertion was present at this time.

*Previous Illness.*—She had had measles at 3 years. She had never had arthritis, "rheumatism" or scarlet fever.

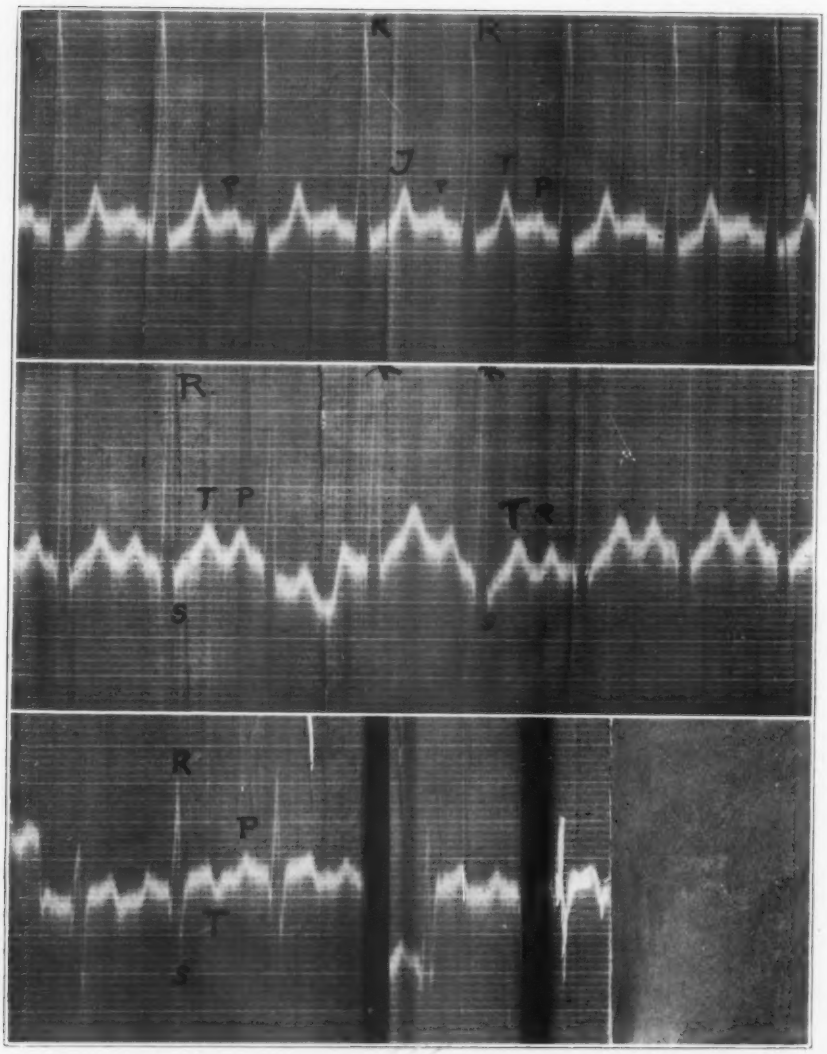



Fig. 4.—Case 1. Electrocardiogram, Leads I, II and III show a pronounced left preponderance, as shown by the high R in Leads I and II and the S of Lead III. Evidence of aortic disease is shown by the very great height of R in Lead II. There is an isolated premature contraction in Lead II (auricular in origin). The T is inverted in Lead III (of no pathologic significance). The P in Leads I and III is wide and notched, a finding in mitral stenosis. P-R 0.16 second; rate 199.

*Family History.*—There was no family history of heart trouble. Both parents were living and well. One older child and two younger children were well. None had had chorea.

*Physical Examination.*—The patient was a rather delicate looking little girl, small for her age, with sallow complexion, apathetic dull look and appearing to be rather weak. The pupils reacted to light and accommodation. The lips showed a capillary pulse plainly. There was a marked visible pulsation of the jugulars and carotids, and over the latter a marked thrill and systolic murmur. In the suprasternal notch, a tumor showing expansile pulsations, synchronous with the heart beat, was plainly seen. A distinct thrill was felt, and a systolic-diastolic murmur heard over it. There was a slight kyphosis and a hollow chest. The expansion of the chest was small but equal on both sides. A moderate right sided scoliosis was present. The lungs were negative.

*Heart.*—The right border was just beyond the right sternal margin; the apex was 2.5 cm. beyond the nipple line and in the sixth interspase. The upper border was at the third rib. The apex beat was diffuse. An oval shaped area of dulness was present behind the manubrium sterni, the apex of which

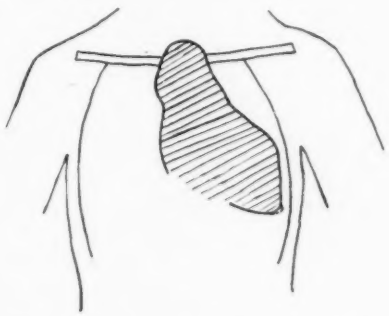


Fig. 5.—Case 2. The shaded portion represents the area of cardiac and aortic arch dulness as determined by percussion and palpation.

was just above the suprasternal notch, extending laterally beyond the margins of the manubrium, and merging into the base of the heart below. At the apex a low pitched, booming, systolic and diastolic murmur was heard, the systolic being stronger. Over the aortic area a rough, loud systolic and a soft blowing diastolic was heard loudest over the third intercostal space to the left of the sternum and transmitted up into the neck and down along the sternum. A visible pulsation was present in all the peripheral arteries. The right radial pulse was smaller in volume and tension than the left.

*Blood Pressure.*—March 17: Right systolic, 115; left systolic, 125. March 23: Right, 115; left, 125. May 5: Right, 135; left, 135.

*Laboratory Findings.*—The stools and the urine were negative. The blood Wassermann was negative. The blood examination revealed a secondary anemia: erthrocytes, 3,848,000; hemoglobin, 62 per cent.; leukocytes, 7,200, of which 5 per cent. were small mononuclears, 26 per cent. were large mononuclears, 68 per cent. polymorphonuclears, and 1 per cent. were eosinophils.

*Diagnosis.*—Chorea; secondary anemia; thoracic aortic aneurysm; chronic endocarditis with hypertrophy of heart.

*Course and Treatment.*—The usual treatment for chorea and anemia was instituted. The patient responded well and left the hospital in three months. Six months later she returned with symptoms of cardiac decompensation. After

four months in the hospital she felt well enough to return home. She returned again two months later with symptoms of cardiac decompensation. This time she did not respond to treatment, and died one month later. A necropsy was not obtained.[19]

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# CONGENITAL MALFORMATIONS OF THE ESOPHAGUS

## WITH REPORT OF TWO CASES *

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Cases of congenital malformation of the esophagus are extremely rare, and many standard works on embryology, anatomy, pathology or pediatrics dismiss the subject with but a few words. In the large necropsy service of Bellevue Hospital, only one case has been recorded in the last sixteen years.[1]

The etiology of the condition still remains in doubt, although several theories to explain it have been brought forward. MacKenzie [2] holds it possible that injury to the ovum or spermatozoa before fertilization may cause the defect. Trauma to the mother or fetus, abnormalities of the placenta, hydramnios and diseases on one or the other parental side, especially syphilis, have all been brought forth as possibilities, but, as Kreuter [3] states, they are not worth serious discussion. Associated malformations are uncommon and most of the children recorded as having esophageal abnormalities were otherwise healthy at birth. Ballantyne [4] calls attention to the fact that the position of the imperforation is practically always at the level of the lower portion of the trachea, and that the gastric portion almost always opens into the trachea. The esophagus, bronchi and lungs all develop from the foregut. Klebs, as quoted by Kreuter, believes that at the common primordium of these structures there is an unequal division of the primitive tissue, the respiratory tree developing at the expense of the esophagus. Plausibility is lent to this theory as the anomaly most often occurs at the bifurcation of the trachea. It is at this point that the primordium for the respiratory organs arises from the foregut.

Krauss [5] believes that the partial obliteration of the esophagus is due to pressure atrophy caused by the primitive arterial vessels crossing

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* From the Department of Pathology and the Children's Surgical Division of Bellevue Hospital.

1. St. George, A. V.: Proc. N. Y. Path. Soc. **18**:32, 1918.
2. MacKenzie, M.: Diseases of Larynx and Esophagus, Philadelphia, Blakiston's Son & Co., 1884, p. 149.
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4. Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene, New York, William Wood & Co. **2**:462, 1905.
5. Krauss, F.: Nothnagel's Special Pathology and Therapeutics, Vienna **16**:96, 1902.

the esophagus in an unusual manner during early fetal life. Kreuter, who reviews all the etiologic possibilties, believes that the esophageal defect is due to arrest of development which means failure of the solid esophageal tube to open. He states that the communication between the esophagus and bronchi is explainable from the standpoint of incomplete separation of the respiratory tract from the foregut. Keibel and Mall [6] state that to produce the common anomaly, the lower

Figure 1

portion of the trachea-esophageal septum must fail to develop, thus leaving the esophagus in communication with the lower part of the trachea.

In reviewing the literature of the subject, MacKenzie, in 1884, collected sixty-three cases. In 1905, Kreuter, including those cases collected by MacKenzie, found 111 in all, and of this number ninety-eight were atresias and thirteen stenoses. Plass,[7] in reviewing the

6. Keibel and Mall: Manual of Human Embryology, Philadelphia, J. B Lippincott Co. **2:** p. 313.

7. Plass: Johns Hopkins Hosp. Rep., 1919.

literature up to and including 1917, was able to find 204 reported cases. Since then Cautley,[8] Apfel,[9] Crowdy,[10] Huntington,[11] Kastner [12] and Shaw [13] have reported one case each, and Brenneman [14] four cases.

The clinical picture is quite definite and the diagnosis is comparatively simple. The child is apparently healthy and swallows liquid readily, but regurgitation occurs in from one to three minutes after swallowing. On taking food, the child becomes cyanotic, often coughs violently, makes gurgling noises, and the vomitus is foamy and alkaline

Figure 2

or amphoteric in reaction. These suffocative attacks are repeated on every attempt to take food. If the patient lives a few days, mechanical dilatation of the upper sac may occur and a few teaspoonfuls of

8. Cautley: Brit. J. Child. Dis. **14**:1, 1917.
9. Apfel: New York M. J. **108**:108, 1918.
10. Crowdy: J. M. Res. **38**:469, 1918.
11. Huntington et al.: Boston M. & S. J. **180**:354, 1919.
12. Kastner: Arch. Pediat. **37**:11, 1920.
13. Shaw: Am. J. Dis. Child. **20**:6, 1920.
14. Brenneman: Am. J. Dis. Child. **16**:143, 1918.

fluid may be retained, but as soon as the sac is full the reflex phenomena recur. A catheter passed into the esophagus under the fluoroscope makes the diagnosis certain.

In the matter of treatment, the only hope of saving the child is to perform gastrostomy as soon as the condition is diagnosed. The technic may be difficult, as the liver may be large and the stomach contracted, as in Case 1, in which there was no tracheo-esophageal fistula. On the other hand, where a tracheo-esophageal fistula is present, as in

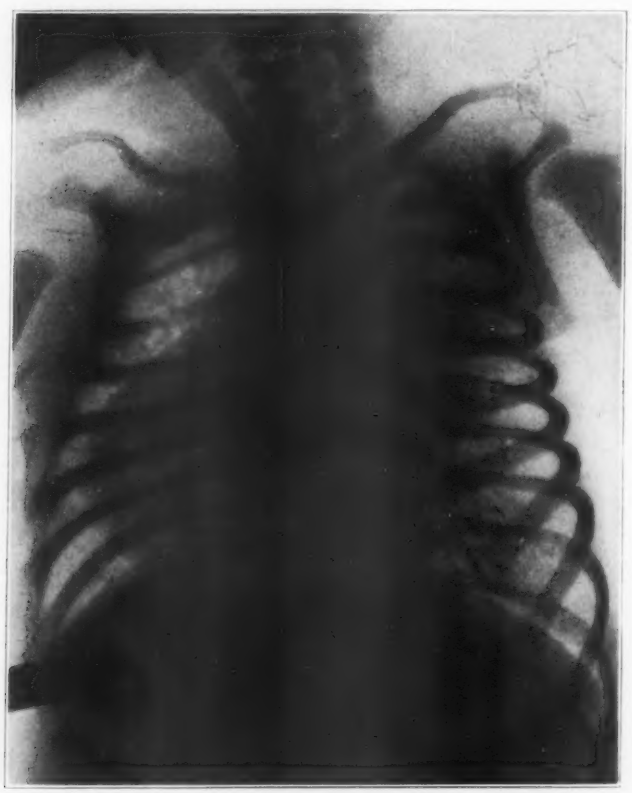

Figure 3

Case 2, the stomach may be ballooned out with gas. Even if the operation is successful, death may result from regurgitation of stomach contents through the tracheo-esophageal fistula into the lungs and there set up an aspiration pneumonia. Following the operation, in Case 2, dark brown fluid was vomited from the mouth; this was undoubtedly stomach contents which had been forced up through the tracheo-esophageal fistula into the trachea and then out through the mouth.

These congenital esophageal malformations have been classified by Whipham and Fagge [15] as follows:

A. Congenital absence of the whole esophagus, a very rare condition.

B. Bifurcation of the esophagus with junction of the two portions near the lower end, only one case reported.

C. (1) Congenital atresia in which the esophagus is divided into two parts, the least rare condition. The upper end terminates blindly in a more or less expanded culdesac. The lower end opens above into the trachea or one of the bronchi, and below in a normal manner into the stomach. The two segments of the gullet are connected by a fibrous or muscular cord.

(2) Much more rarely there is no opening of the lower part into the air passages, the two blind ends being merely jointed by a fibrous band.

D. Stricture caused by a fold of mucous membrane projecting into the lumen of the tube like a diaphragm (a) at the upper part of the esophagus immediately below the pharynx, and (b) near the lower end.

E. Congenital stenosis of the lower end of the esophagus.

Case 1 belongs in the above classification under Group C-2. It is one of the rarer forms of a rare condition. Case 2 belongs under Group C-1—one of the common forms.

## REPORT OF CASES

CASE 1.—*History.*—A baby girl was born of an apparently healthy mother at the Bellevue School for Midwives. Five days later the child was admitted to the Children's Surgical Service of Bellevue Hospital with the diagnosis of hypertrophic stenosis of the pylorus, of the congenital variety. The diagnosis had been made because, without other symptoms, the child had vomited everything taken by mouth since birth. The child weighed about 6 pounds at birth. Regurgitation of fluid taken by mouth occurred within one to three minutes after swallowing. The vomitus was mixed with frothy mucoid material, and was amphoteric in reaction. Bowel movements had been regular and consisted entirely of meconium. Urination was normal.

*Physical Examination.*—The child was markedly undernourished, but otherwise seemed normal, except for the local condition. Examination revealed an apparently normal abdomen. There was the usual easily palpated liver, but no masses, no distention and no peristalsis were visible on prolonged observation. A soft rubber catheter was passed into the esophagus under the fluoroscope. There was no obstruction to its passage about 5 inches from the child's lips and the end of the catheter was seen to be stopped at a point opposite the fourth rib anteriorly, at the level of the transverse part of the arch of the aorta. A diagnosis of congenital atresia of the esophagus at the level of the fourth rib was made.

*Surgical Treatment.*—Although the outlook seemed hopeless, it was thought advisable to attempt to maintain the nutrition of the child by means of a simple gastrostomy. This was done by Dr. Doran under light ether anes-

15. Whipham, T. R. C., and Fagge, C. H.: Lancet **1**:22, 1905.

thesia in twenty-five minutes. A No. 16 soft rubber catheter was inserted into the stomach through its anterior wall. Two purse-string sutures with inversion held the catheter in place. The catheter was brought out through the left rectus in a stab wound made for the purpose. The stomach at the site of the gastrostomy was anchored to the parietes. There was no evidence of pyloric stenosis. The child was considerably shocked and was given stimulation, but died in about three hours.

*Abbreviated Necropsy Protocol.*—The body was that of a white female infant, 5 days old, 50 cm. in length, weighing about 6 pounds. Rigor mortis was absent and there was slight postmortem diffusion over the back. The conjunctivae were clear and glistening. The pupils were widely dilated, equal and regular in outline. A few light colored hairs were present on the head. The fontanels were open, depressed and of normal size. There was no evidence of bony abnormalities of the head or hydrocephalus. The superficial lymph nodes were not palpable. The chest was symmetrical. There was a

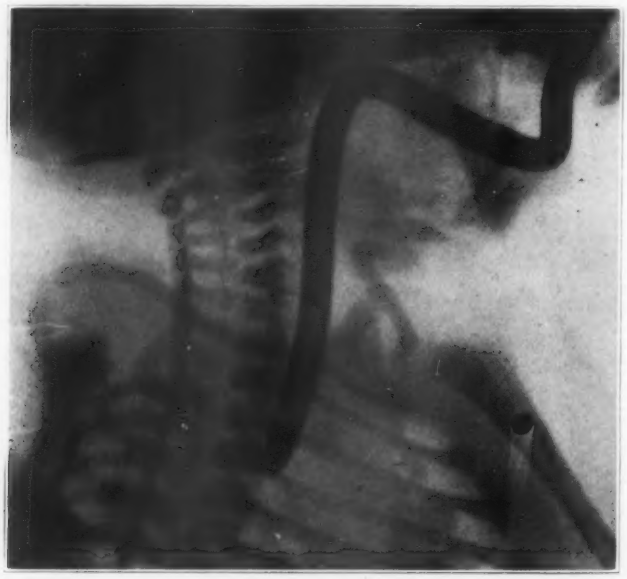

Figure 4

postoperative wound, 3½ inches long, over the right rectus muscle, extending from 1 inch below the costal margin to just below the umbilicus. There was another wound, 1 inch long, with a No. 16 catheter leading from it situated over the left rectus muscle, 1 inch to the left of the midline, and 1½ inches below the costal margin. Both of these operative wounds were fresh and had been sutured with silkworm gut and plain catgut.

On opening the abdomen, the cavity was found to contain large quantities of clotted blood. Some fluid was also present. Near the operative wounds were fibrinous adhesions between the bowels, stomach and anterior abdominal wall. The catheter was found to lead into the stomach, which was sutured to the abdominal wall around the smaller wound. The point of origin of the hemorrhage could not be located, the blood probably escaping, however, from the incision in the stomach.

On opening the chest, the thymus was seen as a mass of pinkish tissue in the upper mediastinum, appearing normal to the naked eye. The pleural

cavities were dry and free from adhesions. The lungs, except for areas of atelectasis at the bases, were natural. The pericardium was smooth and glistening. The heart was normal in size and the endocardium throughout appeared normal. The ductus venosus, ductus arteriosus and foramen ovale were closed, and the normal circulation appeared to have been established. The aorta and pulmonary arteries were smooth and elastic.

The whole intestinal tract, from the cardiac end of the stomach to the anus, was traced and found to be patent. It contained soft, dark meconium. The esophagus was patent as far as the level of the fourth dorsal vertebra, where it ended blindly in a dilated pouch. This pouch was situated just at the bifurcation of the trachea, and just above the arch of the aorta. From this point on, the esophagus was represented as a fibrous band, to within about 1 inch of the stomach, where it again became a patent tube to empty into the stomach. A probe passed up from the stomach showed that this portion ended in a blind pouch about 1 inch from the stomach. No fistula was present between the esophagus and stomach in any part of its course. Microscopic examination of the esophagus showed nothing remarkable.

The other organs revealed nothing worthy of record in the present connection.

CASE 2.—*History.*—A baby girl was born of healthy parents on the obstetric service of Bellevue Hospital. The child at birth presented a malformation of the right forearm which was found to be due to failure of development of the lower two-thirds of the radius. It was noticed a few hours after birth that water given by mouth was vomited at once. The swallowing of fluid was associated with definite asphyxial attacks, lasting about one minute. On attempting to feed the child by gavage, it was found that a soft rubber catheter could not be passed farther than a point 4 inches from the child's lips. The catheter was passed under the fluoroscope and was seen to be prevented in further passage at the level of the third rib posteriorly. A diagnosis of congenital atresia of the esophagus was made.

*Examination.*—The physical examination was negative, except for the above findings, and the presence of a moderately distended abdomen.

The roentgen-ray findings were obtained by giving the child about 2 c.c. of esophagus contrast salt mixture. The radiographer reported a congenital obliteration of the esophagus below a point opposite the second dorsal vertebra. At this point there appears to be a connection between the esophagus and trachea. A considerable amount of contrast salt was introduced into the lungs, outlining the bronchial trees on both sides.

*Surgical Treatment.*—It was decided that gastrostomy offered the only hope of dealing with the condition. This was done by Dr. C. G. Burdick under light ether anesthesia. High right rectus incision revealed at once a much dilated stomach. In the anterior wall a soft rubber catheter was inserted through a small puncture and maintained in position by inverting the stomach with three circular purse-string sutures. The site of the gastrostomy was anchored to the original abdominal wound, which was then closed above the catheter in the usual way. Following operation the child was given small amounts of sterile water and later breast milk by way of the catheter. It was later noticed that the child brought up from the throat a small amount of brown stained material mixed with mucus. The child lived twenty-eight hours after the operation. No necropsy was performed, permission having been refused by the parents.[16]

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# THE USE OF SUPPORTS IN OBSCURE ABDOMINAL CONDITIONS*

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This article supplements our previous paper on bodily mechanics in its relation to cyclic vomiting and other obscure abdominal conditions.[1]

In the first communication it was thought wise not to emphasize the abdominal support but to show the connection between poor bodily mechanics, constipation, cyclic vomiting and acute abdominal pain. Emphasis was laid in that paper on the necessity of a complete medical examination, an examination of the stools and regulation of diet. Especial attention was called to the necessity of rest periods which are ordered for all these patients to prevent and relieve the great fatigue under which they are living. The use of body supports was mentioned but not described in detail because it was felt that undue emphasis would be laid upon the part that the abdominal support plays in the cure of these conditions.

There is unquestionably much danger associated with the indiscriminate use of abdominal supports for children as well as for adults. This paper is written for the purpose of showing the mechanical conditions in which the need of supports is indicated, why they should be used, and the correct method of fitting them to the patient.

The chief purpose of the abdominal support is to relieve the general body fatigue which is always present when the body mechanics are incorrect. When the posture is improper and the child is fatigued, there is always a relaxation of many of the muscles of the body. This is often most evident in the abdominal muscles. When these muscles become relaxed, the abdomen protrudes forward and sags. In this type of child the lower abdomen, that is, the part below the umbilicus, appears larger and has a greater circumference than that above the umbilicus (Fig. 1). The illustrations in the first publication also show this very well.

The following description will be clearer if each factor is studied in Figure 1. Associated with the relaxed, protuberant abdomen there is always an increase in the lumbar curve of the back (lordosis). This lordosis necessitates, by the laws of mechanics alone, even if there were no other elements present, a compensatory forward curve in the

* Received for publication, Dec. 6, 1920

1. Talbot and Brown: Am. J. Dis. Child. **20**:168 (Aug.) 1920.

dorsal spine with a backward displacement of the thorax in relation to the abdomen and hips. This increased forward dorsal curve and backward displacement of the thorax is compensated for by a forward position of the head. The forward position of the head relaxes the accessory muscles of respiration, the sternocleidomastoids, etc., as well as the suspensory ligament of the diaphragm, and allows the chest and sternum to settle downward. This, in turn, relaxes the abdominal muscles, and thus makes possible the relaxed prominent abdomen always present in these cases.

Fig. 1.—This child was referred to the clinic because of very obstinate constipation. Note the characteristic appearance and the very bad bodily mechanics (See text).

This very brief description brings out the fundamental principle that is the basis of all mechanical treatment, namely, that a change in one part of the body is always accompanied by a greater or lesser change in every other part of the body. Just where this change will occur varies, of course, in each individual according to the anatomic type.

In a case of poor bodily mechanics, in which it is necessary to fit a support, one must first consider what part of the body is most relaxed and needs support, and how much of a support is necessary to accomplish the desired results. In order to recognize the abnormal bodily mechanics, it is necessary to have a thorough knowledge of the normal bodily mechanics. This knowledge comes only with experience and careful study of the mechanical principles involved.

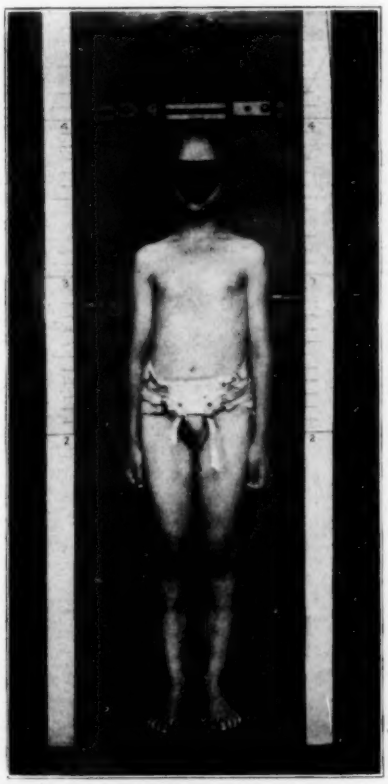

Fig. 2.—Shows child with anterior pad in position.

There are many degrees of abnormality, and it is, therefore, impossible to give any definite rules in regard to the amount of support necessary in cases of poor bodily mechanics as it varies in each individual case, but in general, the greater the fatigue the greater the indication for support, and the larger the support will have to be. The general appearance of a patient will sometimes give an idea of the amount of fatigue present, but in order to form a good opinion, one should always take into account the general factors of habits and hygiene before deciding on the amount of fatigue.

Some postures are so poor that a permanent deformity is associated with the bad mechanics. By permanent deformities we mean such conditions as the curvatures found in structural lateral curvature, forward curved dorsal spine, which is very stiff to extension, or shoulders which droop forward, associated with pectoral muscles contracted because of long standing faulty position of the body. Deformities may occur in any part of the body where the muscles become contracted by long use of an improper position.

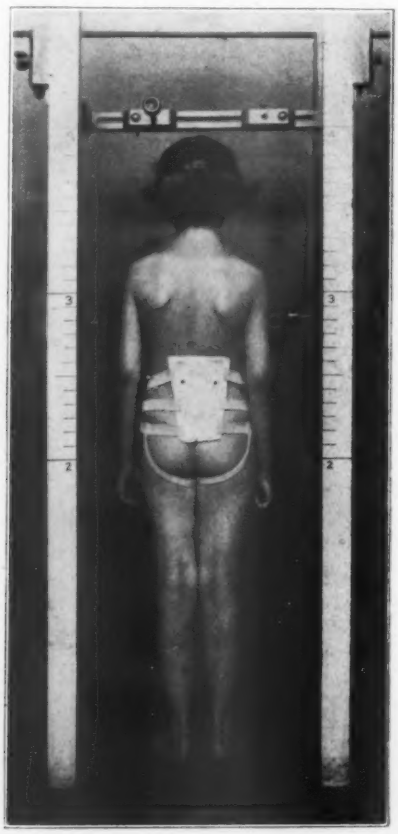

Fig. 3.—Shows child with posterior pad in position.

Two general types of supports may be used: (1) the smaller or so-called anteroposterior pad, which gives support to the abdomen and lower back alone, and (2) the spring back brace, which supports the abdomen, back and shoulders.

The former is usually indicated in mild cases of poor mechanics, or during convalescence from the more severe grades in which a back brace had been used for a time. This anteroposterior pad consists

of two leather pads, one for the front and the other for the back, and is made of two pieces of leather lined with felt. The leather, which is next to the skin, is soft, while the outer piece is somewhat stiffer. The pads are built up on a framework of light steel to which the outside leather and buckles for the straps may be attached. The front pad is made in the shape of a parallelogram with the two lower corners cut off so that it will fit below the umbilicus and over the

Fig. 4.—Shows now the anteroposterior pad tends to improve the mechanics of the abdomen. The improvement of the bodily mechanics as a whole can only be accomplished by postural education. Compare with Figure 1.

muscles of the lower abdominal wall (Fig. 2). The back pad (Fig. 3) is also the shape of a parallelogram, except that the upper end is wider than the lower end. The pad should be made long enough to extend from the cleft of the buttocks to the eleventh or twelfth rib. This is of great importance. If it is made too short, the upper body will be able to lean backward over the top of the pad, thus causing an

increase of the lumbar curve, and although apparently effecting what is desired for the abdomen, it would intensify the original anteroposterior curve and do harm to the patient.

The pads of this anteroposterior belt are connected by three straps. The top strap should come just above the iliac crests (Fig. 4), and the bottom strap placed at the sides, so that it will come just between the trochanter and the crest of the ilium. The perineal straps are fastened to the bottom strap, at a point just back of the trochanters

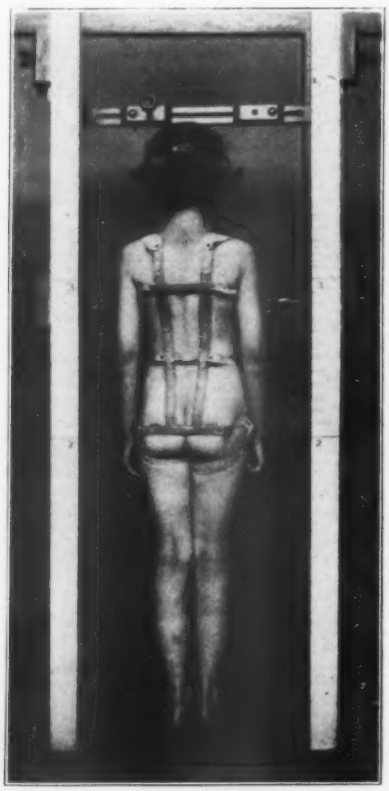

Fig. 5.—Shows the spring back brace on the child (rear view).

for the purpose of keeping it from slipping up on the abdomen. This anteroposterior belt should be worn snugly. Educational exercises should be given at the same time.

The other support, that is, the spring back brace, is made of a tempered spring steel about 18 to 20 gage and is covered with felt and leather. The measurements for the steel are taken from the lower end of the sacrum to about one inch above the spine of the scapula (Fig. 5). There are two uprights, from one and a half to two inches

apart at the bottom, and from three to four inches apart at the top, or enough to make the uprights come over the scapulae and not directly over the erector spinae muscles. There are three crossbars, one at the bottom, to which is fastened the lower strap of the front pad, worn in connection with the brace; a second one at a point just above the crests of the ilia, to which is fastened the top strap of the front pad, and one at the top placed at the level of the axilla behind or about one inch above the lower border of the lower angle of the

Fig. 6.—Shows child with spring back brace on. Compare with Figure 1 and note the change in the bodily mechanics.

scapula. This position is important because if it is too low the scapula will have a tendency to ride up on the crossbar and be very uncomfortable.

This brace is usually made up in the rough at the shop and sent to the orthopedic surgeon to be fitted to the child before the steel is tempered. The fitting is a matter of considerable importance and should never be left to the instrument maker. The main point to be

remembered in the fitting of the brace is that it is applied to prevent the child from assuming the habitual extremes of the faulty mechanical positions, and it should, therefore, be fitted to the child with the body in the best position that can be assumed. Since the brace is made of spring steel it consequently allows a considerable amount of motion, at the same time preventing the extreme faulty position (Fig. 6).

We wish to emphasize again that neither of the braces described will permanently prevent the child from assuming the faulty postures

Fig. 7.—Note the extreme faulty posture, especially the flat chest and the abdomen that is more protuberant below the umbilicus than above. This child is Case 2 of our previous communication. Compare with Figure 8.

and they are not put on with that idea in view, but merely to rest the child by lessening the amount of muscle strain, and to help correct the faulty habits of posture.

The wearing of the braces should always be accompanied by educational exercises, except in the case of very young children. These exercises are planned primarily to teach the child how to use its body

in good mechanics and secondarily to strengthen or increase the size of the muscles. Since the child is fatigued to a greater or less degree as a result of the poor body mechanics, rest is much more important than exercise, and for the first week, at least, the child is asked to lie down with a pillow under its lumbar and lower dorsal spine so that the ribs are expanded while the head and buttocks rest on the table. Breathing exercises can be performed in this position and help stretch the contracted chest.

Fig. 8.—Shows the same child as shown in Figure 7 after postural training. Note the change in the shape of the abdomen caused by contraction of the abdominal muscles. Also the flattening of the lumbar curve which is accomplished by gluteal contraction. Note also the position of the head.

The next step is to teach the child the correct standing position. In this procedure, two separate groups of muscles are used which must come into play before it can be accomplished successfully. First, the child must learn how to contract the gluteal muscles. This will flatten the lumbar spine. Second, the muscles of the lower abdomen, below the umbilicus, should be contracted, thus pulling in the lower abdomen and forcing the intestines upward into their normal position. This will relieve the strain on the mesentery. Finally, holding this position, the head should be held up straight with the chin in. This will draw up the chest to its proper position. After the child has learned how to

control the muscles involved in these movements and can assume a correct standing position, other exercises may be given. The exercises should always be done with the body in good posture. If the correct posture cannot be maintained, the exercises should not be considered beneficial since the prime object of all the exercises is simply to educate the child to use its body in good mechanics. Figures 7 and 8 show the results which may be obtained by postural training supplemented by temporary use of the brace.

## CONCLUSION

In conclusion we wish to emphasize again the fact that mechanical supports are only temporary makeshifts, the purpose of which is to break up the bad habits of posture and relieve the fatigue. They should, of course, be dispensed with at the earliest possible moment. Education of the muscles is in reality the most important element in the treatment, but it often has to be accomplished with the aid of mechanical supports until the muscles are strong enough to take up the burden themselves. When possible, treatment should be carried out without the use of supports.

# KERATOSIS DIFFUSA FETALIS (ICHTHYOSIS CONGENITA)*

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## NOMENCLATURE

The term "ichthyosis," derived from the Greek word ἰχθύς (fish), has been used to designate keratosis, a condition in which the skin bears a fancied resemblance to the skin of fishes. It is, however, only in rare cases that the skin resembles somewhat the fish skin, the comparison appearing to be far fetched in the majority of cases of keratosis, both in the mild and in the severe variety. In the latter, the skin has more properly been likened to tortoise shell; skin of a baked apple; skin of potatoes cooked in water; dry yellow leather (morocco leather); armor of crustaceans, bark of trees, skin of a serpent, crocodile skin, etc. A number of names for these conditions have been derived from the gross appearance of the skin such as ichthyosis, fish skin disease, xeroderma (dry skin), xeroderma ichthyoides, sauriasis, crocodile skin, alligator skin, harlequin fetus. Riecke [1] made the most thorough recent study of the condition and gives the literature to 1900. Ballantyne's [2] book gives the older bibliography.

All these terms are based on a predominating and most striking symptom of the condition. It is, therefore, the variation in the intensity of the symptom which varies the name of the disease from ichthyosis to sauriasis or xeroderma. This nomenclature leads to a great variety of terms, each of which emphasizes a special predominating symptom or gross pathologic condition of the skin and conveys the idea that this predominating symptom is the essential component of the condition. It ignores the pathologic anatomy which is common to all these conditions, at least qualitatively, and which is the essential change, the variations in the clinical picture depending on the severity of the pathologic changes.

A number of names derived from the pathology of the condition have been proposed to designate what has been called "ichthyosis."

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* From the Sarah Morris Hospital for Children and the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital.

1. Riecke: Ueber Ichthyosis congenita, Arch. f. Dermat. u. Syph. **54**:289, 1900.

2. Ballantyne: The Diseases and Deformities of the Fetus. Edinburgh, Oliver & Boyd, 1892-1895.

Among these are keratosis diffusa epidermia intrauterina (Lebert), because the main seat of the histologic processes is in the epidermis and the most striking is the enormous hyperplasia of the stratum corneum; universal diffuse keratoma (Kyber); hyperkeratosis diffusa congenita (Eppinger).

Keratosis may be defined as an abnormal cornification of the skin and, theoretically at least, keratoses may be classified as hypokeratosis and hyperkeratosis (quantitative abnormalities), and parakeratosis or dyskeratosis (qualitative abnormalities), and a combination of quantitative and qualitative abnormalities. Most of the affections classified under the keratoses consist of increased and abnormally altered cornification. The term keratosis is more appropriate than hyperkeratosis to designate the affection that has been named "ichthyosis," since this condition is a combination of hyperkeratosis and parakeratosis.

The two affections which have been called ichthyosis simplex (or vulgaris) and ichthyosis congenita are generally admitted to be congenital affections, some regarding them as congenital anomalies of the development of the skin. The term "congenita" therefore, is not only superfluous, but it leads also to confusion, conveying the idea that one form is congenital and the other form (simplex, vulgaris) not congenital, which, however, is not the case. Since, further, the affection which we are about to describe, develops during fetal life and is almost always diffuse, in contradistinction to the simplex form, which as a rule develops during the first year of life and usually is not universal, we believe that this keratosis should be designated "keratosis diffusa fetalis," under which term we are going to describe the affection.

## DEFINITION

Keratosis diffusa fetalis may be defined as an independent congenital developmental anomaly of the skin, of unknown etiology, characterized by diffuse, usually general hyperkeratosis and qualitatively abnormal cornification of the skin with decreased exfoliation of the epidermis. This combination of processes causes the formation of thick horny scales with intervening deep fissures, the skin resembling a horny cuirass. Secondarily, it results in arrest of development and in deformities of the external ears, eyes, nose and lips, the latter symptoms usually being already present at birth; occasionally, however, they may be very slight or entirely absent at this time. The condition usually terminates fatally even in the absence of any assignable cause.

## SYMPTOMS AND CLINICAL TYPES

The most characteristic in the clinical picture of this condition are the skin changes and the secondary malformations of ears, eyelids,

nose and lips. The course of the disease depends primarily on the intensity of the skin changes. Basing his classification on the intensity of the skin changes, especially as seen at birth, Riecke divides the cases of keratosis diffusa fetalis into three types.

*Keratosis diffusa fetalis* (ichthyosis congenita par exochen, Riecke) comprises the cases with high grade anomalies of the skin and with resulting disturbances of growth. In these cases the condition is

Figs. 1, 2 and 3.—View of whole infant, illustrating the external characteristics.

already fully developed at birth, presenting a fairly constant and uniform clinical picture and these children are not viable. The longest period of life which was observed was 9 days (Jahn [3]). On the average, the infants died after three days, and only rarely were they

3. Jahn: Ueber Ichthyosis congenita. Inaug. Diss., Leipzig, 1869.

born at full term. The fetuses or infants belonging to this group may be described about as follows: The entire surface of the skin is formed by thick, tough, horny shields and plates, mostly of yellowish gray color, and about 0.5 cm. in thickness. They are of manifold configuration, round, oval, triangular, quadrangular, rectangular and of different sizes. Between the plates there are numerous fissures

Fig. 4.—Face, neck and hands of patient.

varying in width and depth, sloping down either abruptly and almost perpendicularly from the plate, or a gradual, slow transition takes place. Some fissures are provided with a thin epithelial covering; frequently, however, the corium is freely exposed. Hands and feet take no part in the formation of plates and fissures. In most cases the hands and feet are clubbed and they are covered by smooth, shiny,

tough, thickened skin. The genitals are normally developed in some cases, in others they are rudimentary. Ectropion of their skin folds is the rule.

Just as typical as the abnormal condition of the skin are the anomalies in the form of the face that are found in the individuals belonging to this group. Lanugo hair covering is frequently absent, and cilia and supercilia frequently do not develop. The eyelids are rudimentary in the shape of horny plates, and in the position of extreme ectropion, so that the conjunctiva is prominent in the shape of red, raw tumors below which the otherwise normal eyebulb is hidden. The

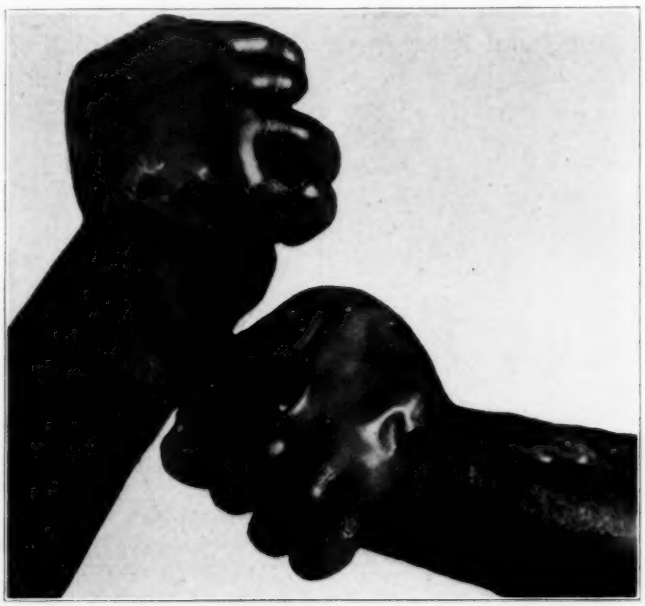

Fig. 5.—Hands of patient.

nose is flattened, frequently barely rising above the level of the surrounding skin of the face. The nasal openings are narrowed and occasionally only one is found patent. Both lips are highly ectropied, so that both alveolar processes are well seen. The mouth is continuously open, resembling thus the mouth of fishes. The lobules of the ears are never distinctly developed. Occasionally the formation of the ear is indicated only in the skin of the ear, the lobules of the ear being as in bas relief. The presence of the auditory canal may in most cases be demonstrated by sounding only, since it is a very narrow fissure.

The infants born with severe keratotic changes of the skin, as described above, persistently hold their extremities in the fetal attitude. There is very little movement and the breathing is shallow, almost imperceptible. The mouth cannot be closed, nor opened any wider, and this condition markedly interferes with proper nursing. The stiffened condition of the skin is undoubtedly responsible for the diminished mobility of the infant.

Almost one-half of all cases of keratosis diffusa fetalis belong to this group.

*Keratosis diffusa fetalis mitior* (ichthyosis congenita larvata, Riecke) comprises those cases in which the condition is not fully developed at birth, the degree of development especially of the skin changes varying in different cases. While all the children of the first group die in a few days, those of the second group may survive for a

Fig. 6.—Soles of feet.

much longer time. About one-half of these children were born premature, the other half being full-term infants. While the clinical picture presented by the cases of the first group is fairly uniform in symptoms and clinical course, there are considerable differences in the intensity of the changes in different cases and, therefore, also in the course of the disease in the second group. The intensity of the process often varies in different regions of the body.

In some cases, while there are marked anomalies in the formation of the face, the skin may be of more or less normal appearance. In other cases, plate formation and fissuring of the integument is the most striking symptom, while the face shows only very little abnormality. Or, on the other hand, the slightly scaling skin presents numerous folds all over the body, so that it appears to be loose and

too wide; on the extremities, however, it may be tightly adherent to the subcutaneous tissue, thin, shiny and desquamating in large flakes. Frequently the skin all over the body is thin, atrophic, parchment-like, dry, shiny and traversed by fissures and furrows, and covered with scales of tissue paper character. To this latter condition refers the comparison to thin collodium film made by many authors or to a coat of varnish or to cracked porcelain glaze.

There may also be considerable variation in the intensity of the anomalies in the development of the face. Extreme ectropion of the upper lip may be present while the lower lip may be more or less

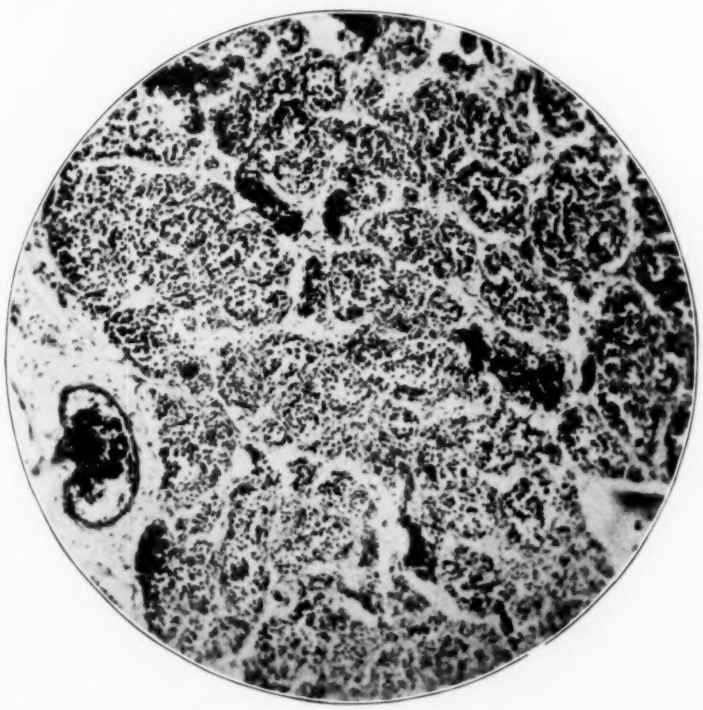

Fig. 7.—Thyroid. The tissue is undifferentiated. Photomicrograph, × 110.

normal. A high grade ectropion of the eyelids may be present, while the nose and the ears may be normal in their appearance. Or with a well formed nose, the lips may be markedly everted and every trace of the ear lobules absent; or with a normal development of the latter, the deformity of the nose may be the most striking symptom.

The third group, *keratosis diffusa fetalis tarda,* (ichthyosis congenita tarda, Riecke) is marked less by its clinical peculiarities than by its peculiar clinical course. In the cases belonging to this group,

the above described anomalies are only slightly developed at birth, or the infants may be born without any visible changes on the part of the skin or of the face. The viability of these infants, provided they are not born prematurely, is scarcely influenced by the condition. Only after days, weeks or months the symptoms develop which finally lead to the picture of milder keratosis diffusa fetalis. It is remarkable in these cases that with the development of the external anomalies the general development of the entire organism almost always suffers. The further existence of these cases depends on the final degree of development of the keratosis provided no intercurrent condition causes death, and the individuals may remain alive for months or even years.

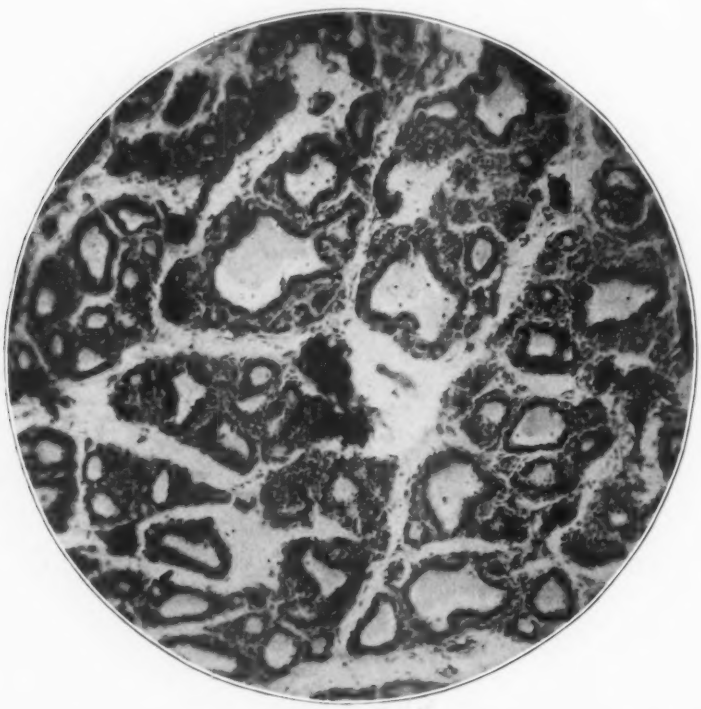

Fig. 8.—Thyroid. Differentiated, functioning follicles in one of the four small areas of such tissue present. Photomicrograph, × 110.

There is a striking similarity, not only in the condition of the external integument and of the formation of the face, but also in the clinical picture, in that the anamnesic data are almost the same. The abnormal condition of the skin was noticed immediately after birth or, on the other hand, after a longer period, mostly of several years duration.

Two cases reported by Munnich [4] belong to this group. Two children of the same family were affected, and it is interesting that the appearance of the affection was preceded by redness of the skin, which has also been observed by Haus [5] in paratypical ichthyosis and many horny nevi. At the time of birth, the condition was only very slightly developed and longer life was possible.

Fig. 9.—Skin of the back. A central group of three elongated papillae is covered above by the greatly thickened horny layer, only the lowermost layer of which is shown, and is separated on each side from the neighboring groups of papillae by large, whorllike masses of keratinized epithelium. Photomicrograph, × 110.

Lang [6] reported the cases of two children in the same family. The older child was prematurely born, and the first symptoms of the disease appeared in the third week, while in the other child, born at full-term, the affection began in the second month of life. In these two children, features characteristic of keratosis diffusa fetalis were

4. Munnich: Monatsch. f. prak. Dermat. **5**:240, 1886. (See Riecke, Ref. 1.)

5. Haus: Ichthyosis congenita (hyperkeratosis diffusa congenita). Norsk. Mag. f. Laegvidensk. **16**:542, 1901.

6. Lang: Tageblatt d. 58 Versamml. deut. Naturfursch. u. Aertzte in Strassburg, 1885, p. 295 (See Riecke, Ref. 1).

later seen, namely ectropion, involvement of the eyes, deformities of the ears, and of the anus, absence of panniculus, parchment-like skin, flexion contractures, shortening of the fingers with deformity of the nails, and disturbances of the general growth. Abscesses appeared, and death occurred at the age of 27 and 15 months, respectively.

Róna's [7] cases are of special interest because of the fact that the author was able to observe personally the development of the process and did not have to rely merely on anamnesic data that are not always reliable.

Fig. 10.—Skin of the back. The epidermal covering of the elongated papillae. The transition from nucleated to nonnucleated epidermis is very abrupt. The deeper half of the nonnucleated portion contains fine hematoxylin staining granules. Photomicrograph, × 230.

The cases of the third group show in their course a certain relationship to other forms of keratosis, e. g., keratosis palmaris and plantaris (Bruhns,[8] Dore [9]), which become noticeable in the first weeks

7. Róna: Hochgradige Ichthyosis im Säuglingsalter, Arch. f. Dermat. u. Syph. **21**:339, 1889.

8. Bruhns: Die atypischen Ichthyosfälle und ihre Stellung zur Ichthyosis congenita und Ichthyosis vulgaris. Arch. f. Dermat. u. Syph., **113**:187, 1912.

9. Dore: A Case of Congenital Hyperkeratosis of Palms and Soles, Proc. Roy. Soc. Med., London **7**:35, 1913.

of life, but reach the highest degree of their development only after several months. In this respect they remind one of certain keratoid nevi, of which usually nothing is seen at birth. Some, at least, of the cases of ichthyosiform erythroderma, which have been collected and analyzed by MacKee and Rosen,[10] appear to belong to this group.

### PATHOLOGY

Marked pathologic changes are almost entirely limited to the epidermis, the most characteristic being hyperkeratosis, the cutis showing only slight inflammatory changes (Wassmuth [11]), which may well be

Fig. 11.—Skin of the back. The skin at the bottom of one of the fissures. The entire thickness of the horny layer is shown. The cellular epidermis is thin and the papillae are short, widely separated and oblique. The deeper tissue is edematous. Photomicrograph, × 125.

due to secondary infection. In a few cases pathologic changes have also been found in glands of internal secretion (thyroid, thymus, suprarenals). Interesting is also the intense congestion of many organs of

10. MacKee and Rosen: Erythrodermie congénitale ichthyosiforme. Report of Cases with a Discussion of the Clinical and Histologic Features and a Review of the Literature, J. Cutan. Dis. **35**:235, 343, 511, 1917.

11. Wassmuth: Beitrag zur Lehre der "Hyperkeratosis diffusa congenita," Beitr. z. path. Anat. u. z. allg. Path. **26**:19, 1899.

the body (kidney, liver, meninges of the brain, etc.) similar to that occurring after severe burns where a large portion of the skin is destroyed. In most cases no particular pathologic change or group of changes was found that could be designated as a direct or ultimate cause of death.

Epidermis, dermis and subcutaneous tissue were found to be present in all cases, the subcutaneous tissue and the dermis being either normal or showing slight secondary changes. The different layers of the epidermis are more or less preserved, and Wassmuth differentiated even five layers of the epidermis. His observation, however, has not been confirmed by other investigators.

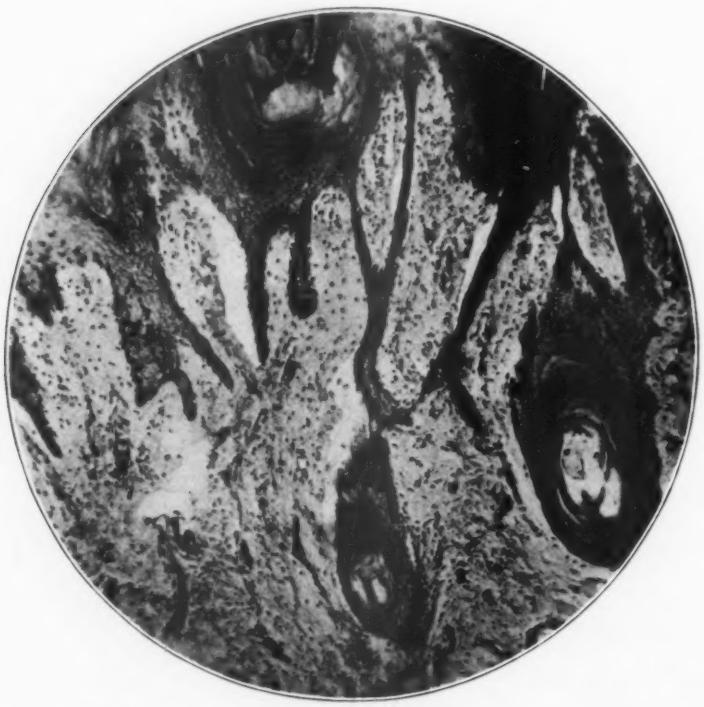

Fig. 12.—Skin of the scalp. The papillae are very long, branched and edematous. The cellular epidermal layer is very thin. Two hair follicles are shown, one of which is almost completely cornified. The greatly thickened stratum corneum is not shown. Photomicrograph, × 90.

Enormous thickening of the stratum corneum is the most striking and the most constant pathologic change. Its thickness varies in different regions of the body, being thinnest on the abdomen (0.2 mm.) and thickest on the scalp (up to 5 mm.), averaging about two hundred times thicker than normal (Wassmuth).

According to some authors (Schabel,[12] von Schab [13]) the stratum corneum is homogenous, bearing, however, a distinct indication of its elementary structure. Claus [14] has observed nuclei and nuclear remnants in this stratum. Wassmuth found it to be very irregular in structure, composed of lamellae superimposed in wavelike manner and in general parallel to the surface, and of layers with keratohyalin and keratin granules. Other authors (Koller,[15] Stühlinger [16]) were able to demonstrate cellular structure only in the lowermost layers of the stratum corneum. Jahn [8] has isolated flat epidermal cells from this layer. Riecke thinks that it is a mistake to regard the horny deposits as homogenous, but he remarks that he found the stratum corneum to be completely developed, although the fetus was premature. Unna [17] says that the horny cells are homogenous and contain no nuclear remnants which are normally present.

Meyenburg [18] states that qualitatively the horny layer seems to be similar to that found on the palm of the hands and the soles of the feet, therefore of normal chemical composition and only excessive in amount, i. e., simple hyperkeratosis. Wassmuth, on the basis of differential staining methods and of digestive experiments, comes to the conclusion that the epidermic horny plates are not formed of normal corneal substance, but rather by cells in the stage which immediately precedes cornification. Von Bärensprung [19] found that these plates contain large quantities of ash and especially of iron and silicates. Riecke states that although there are some deviations from the normal in the nature of staining of the stratum corneum, this method does not furnish a sufficiently safe basis for estimation of cornification of this layer, nor for the formulation of a hypothesis as to the development of this anomaly, and that the elements composing the horny deposits proved to be, wherever they could be recognized, always ordinary horny cells and by experiments with digestive tests their nature in all horny plates may be proven.

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12. Schabel: Ichthyosis congenita. Inaug. Diss., Tübingen, 1856.

13. Von Schab: Drei Fälle von congenitaler Ichthyose. Inaug. Diss., München, 1889.

14. Claus: Ichthyosis congenita. Inaug. Diss., Berlin, 1897.

15. Koller: Ein Fall von Ichthyosis congenita. Inaug. Diss., Leipzig, 1894. (Unpublished thesis; see Riecke).

16. Stühlinger: Ein Fall von Ichthyosis congenita. Inaug. Diss., Marburg, 1880.

17. Unna: The Histopathology of the Diseases of the Skin. Translated by Norman Walker. Edinburgh, W. F. Clay, 1896.

18. Meyenburg: Ein Fall von Ichthyosis congenita. Inaug. Diss., Berlin, 1912.

19. Von Bärensprung: Die Hautkrankheiten. Erlangen, F. Enke, 1859.

Meyenburg found cell remnants and enclosed masses of detritus in the stratum corneum, but he has observed neither enclosure nor displacement of epithelium. Almost all other authors, however, who have studied the histopathology of this condition have found structural abnormalities and peculiar and interesting formations, consisting of concentrically arranged lamellae of horny cells enclosing (1) excretory ducts of sweat glands, (2) hair follicles and hairs, (3) structureless material, (4) empty spaces.

The mouths of the excretory ducts of sweat glands are surrounded by concentrically arranged layers of corneal cells and the cells lining the ducts are hornified on their course through the epidermis. In some of the ducts cornification of the epithelial cells may be observed for some distance into the cutis, this causing the formation of cylinders composed of concentric layers of cornified cells. Depending on the direction of the section and its relation to the lumen of the duct, various pictures may be produced, the lumina appearing circular, oblong, or irregularly compressed from the sides and assuming various forms. Frequently several excretory ducts are found in one system of concentric lamellae.

The mouths of hair follicles and of sebaceous glands are also surrounded by concentric layers. In the scalp the layers of horny cells in the stratum corneum run in every direction, but around the hair they are always concentrically arranged. The cornified cells invade the ducts of the hair follicles, but usually only to the mouths of the sebaceous glands, and cylinders similar to those seen in connection with the sweat glands are formed. In these cylinders hairs may have a straight or wavelike course. Wherever these cylinders lie close together the spaces between them are occupied by more or less solid horny lamellae, which are continuous and connect together the horny cylinders of the hairs. In places where the hair is more scanty, the sections of the horny cylinders are farther apart, and surrounding them and binding them together are massive layers of horny cells which usually show a wavelike stratification parallel to the papillary surface. Often several horny canals are so close together as to form a bundle. The direction of the cylinders is never vertical to the surface, but always markedly oblique, often almost horizontal.

Besides the systems of concentrically arranged lamellae enclosing ducts of sweat glands and hair follicles, concentric lamellae are seen enclosing deposits of a more or less homogenous mass. These deposits are of various shape and irregularly scattered throughout the stratum corneum. They have been seen by many observers, but there is a wide diversity of opinion as to the nature of the material enclosed

within the concentric rings of the lamellae. Moore and Warfield [20] regard the enclosed material as degenerated epidermal cells. Meyenburg regards these deposits as cell masses and enclosed masses of detritus. Jahn thinks that the contents of these enclosures is sebum and he states that he has found these accumulations both in the cutis and in the epidermis. Other authors (von Schab, Schabel, Stühlinger, Müller [21]) regard them also as products of sebaceous glands. Riecke, however, says that on the basis of his studies he believes that the possibility of these masses being secretion of sebaceous glands or fatty masses is entirely out of the question. He explains the development of these enclosures as follows: The cutis sends out projections into the horny deposits. The projections first become edematous, later completely degenerated and then changed into desiccated necrotic masses; the rete malpighii (stratum germinativum), becoming more and more slender, finally cornifies. Such enclosures may still remain connected with the processes of the cutis. Due to the direction of the section, however, they appear often as isolated enclosures. Moore and Warfield remark that some of these enclosures look not unlike the cell nests of epithelioma.

Concentric lamellae enclosing empty spaces in the corneal layer have been seen by Moore and Warfield. Riecke says that in a number of cases irregular, more or less slitlike interstices were observed in the corneal layer, which, however, have been found to be artefacts due to the shrinking of the tissue in alcohol.

It is remarkable how suddenly the hyperkeratosis stops at the mucocutaneous junction. Moore and Warfield describe this striking phenomenon as follows: "In the section of the lip the mucous membrane on the buccal side is quite normal. On the exposed portion of the lip there is a small amount of horny material, which at the junction of the lips and of the skin suddenly becomes enormously thickened, having all the characteristics described above. The abrupt change is rather remarkable, as if there were an invisible barrier extending deeply into the skin, beyond which the disease process could not extend."

The tissue covering of the fissures intervening between the horny plates varies in its histologic structure. Some of the fissures have no epidermal covering, the cutis being directly exposed. From this one may conclude that these fissures are of so recent development that the epidermis has not had time to cover them. Other fissures possess epidermal covering which, however, in most cases is very thin and

20. Moore and Warfield: Fetal Ichthyosis: Report of a Case with Pathological Changes in the Thyroid Gland, Am. J. M. Sc. **131**:795, 1906.

21. Müller: Ichthyosis congenita, Verhandl. d. Phys.-med. Gesellsch. in Würzburg **1**:119, 1850.

devoid of hair follicles and glands, their rudiments being present occasionally. Riecke states that all the skin fissures that he has studied in two of his cases possessed epidermal covering. The horny layer of the fissures he found moderately thickened in its central portion, increasing in thickness laterally.

Statements of different authors vary as to the presence or absence of stratum lucidum. Riecke says: "in many pieces of the skin above the stratum granulosum a layer of horny cells corresponding to the stratum lucidum and composed of one to two rows of cells may be demonstrated, which in most stained specimens may be well differentiated by its lack of keratohyalin on the one hand and the vesicular nature of its cells on the other from the granular layer and the following layer of the massed horny cells. This layer, however, is not constant." Meyenburg states that the "stratum lucidum and stratum granulosum are united." Other authors, while not making any positive statements about the stratum lucidum, say that the stratum corneum is formed directly from the stratum germinativum (Unna, Moore and Warfield, etc.).

According to Riecke, the stratum granulosum is of normal thickness and the formation of keratohyalin, corresponding to the different regions of the body, shows only physiologic variations in intensity. Wassmuth was able to demonstrate the stratum granulosum in the scalp only. According to Meyenburg "stratum lucidum and stratum granulosum are united."

Riecke found no structural anomalies in the stratum germinativum. The epidermal covering of the fissures was thinner than in those regions of the skin that are covered by horny plates. Moore and Warfield are of the opinion that this layer is thinned. At a little distance from the fissures, the cells of the stratum germinativum were found to be small and compactly arranged. Very near the fissures, however, the cells of this layer were found to be larger, pale, separated from each other somewhat, and many mitotic figures were seen. They regard this as an effort on the part of nature to bridge over the gap. In no other places were mitotic figures seen in the stratum germinativum. Wassmuth says he found the stratum germinativum to be moderately thickened, the cells of the epithelial pegs assuming spindle form, but nearer to the surface becoming polygonal. Galewsky speaks of "new formation in the rete."

As to the condition of the dermis (cutis, true skin) the statements of authors vary considerably. It is said to be of normal thickness (Schabel, von Schab, Wassmuth) or generally thickened (Claus, Jahn, Stühlinger). Hypertrophy of the papillae was seen by many authors

(Bruck,[22] Claus, Jahn, Koller, Schabel, Straube[23]). Unna considers the papillary changes secondary to the hyperkeratosis.

The histologic structure of the dermis was found to be normal in almost all cases. Abundant accumulation of lymphoid and of round cells, combined with hyperemia and suggesting inflammation, were observed by Claus, Jahn, and Brandweiner.[24] Wassmuth states that he has found in the derma only an insignificant chronic inflammation of low grade. The blood vessels of the derma were found to be dilated by Bruck, Claus, Jahn, Lassar,[25] Koller, Straube, Bossert,[26] and of normal size and arrangement by Riecke. As compared with the normal skin, the papillae were much more numerous, broader and flatter, with greater irregularity in form and size (Riecke). Daniel and Cordes[27] state that the corium is edematous and contains less elastic tissue than normal, the papillae of the corium are hypertrophied, and their blood vessels are widely distended with blood. Riecke, on the other hand, states that wherever elastic tissue was studied, it was found to be normal. Moore and Warfield, however, make a statement that "in sections, stained with Weigert's elastic tissue stain the elastic fibers appear to be decreased in amount, and in many places are ruptured. . . . The true cutis is in most places normal in appearance. The papillae following the contour of the rete mucosae are in places elevated, but, on the whole, do not seem as large as normal. In some places there are collections of cells, lymphocytes and plasma cells, in great numbers, and it looks somewhat like embryonal connective tissue. The fat in all sections is decreased in amount. The leukocytes are few in number even where the skin is fissured. All the blood vessels are markedly congested, but are not thickened."

The subcutaneous fat tissue was well developed almost everywhere, although not excessive, in both of Riecke's cases. The blood vessels and nerves traversing this layer, showed no pathologic changes. It was found somewhat less developed by Claus, Firmin,[28] Koller, and found to be somewhat thicker by Gerstenberg.[29] According to Daniel

22. Bruck: Ein Fall von Ichthyosis congenita. Inaug. Diss., Berlin, 1888.
23. Straube: Ein Fall von Ichthyosis congenita. Inaug. Diss., Marburg, 1883.
24. Brandweiner: Die Hautkrankheiten des Kindesalters. Leipzig u. Wien, Franz Deuticke, 1910.
25. Lassar: Demonstration eines Präparates von sogenannter Ichthyosis congenita, Berl. klin. Wchnschr. **23**:836, 1886.
26. Bossert: Kasuistischer Beitrag zur Ichthyosis congenita. Jahrb. f. Kinderh. **82**:216, 1915.
27. Daniel and Cordes: Case of fetal ichthyosis, J. A. M. A. **35**:1081 (Oct. 27) 1900.
28. Firmin: Contribution à l'étude de l'ichyose foetale. Thèse, Paris, 1899.
29. Gerstenberg: Zur Pathologie der Ichthyosis congenita, Deutsch. Arch. f. klin. Med. **57**:263, 1896.

and Cordes, panniculus adiposus is everywhere poorly developed, being absent in places (due to prematurity).

There is a wide diversity of opinion among authors as to the condition of the sweat glands, and the statements vary from "entirely normal" to "total absence or atrophy." Carbone [30] and Riecke found them to be normal, except for the cornification of their ducts. Daniel and Cordes and Wassmuth state that they are increased in number, but otherwise normal. Claus and Stühlinger report that they found the sweat glands hypertrophied, while Straube reports their complete absence. Meyenburg says that there are no sweat glands in the skin of the body, but in the skin of the palms and soles they are increased in number. Koller found them absent, but he observed well developed excretory ducts in the palms and soles. Here the excretory ducts of the sweat glands present an especially characteristic appearance which was first described by Müller [31] and confirmed also by many other authors. He described their course as follows: "After they have risen in their ordinary spiral course for some distance, they assume a straight course and all of them bend so sharply to one side that they lie almost horizontally to the epidermis. Thus they approach the surface gradually and near the surface they become curved again. Thus ten to fifteen or even more straight horizontal canals are situated above each other and this causes the finely striated appearance of the epidermis." Riecke says that the sweat glands and their ducts were found to be normal with the exception of that portion of the duct which runs through the epidermis, this portion being enclosed in a horny cylinder described above. The number of the sweat glands he states to be normal, although some authors have reported an increase in number in palms and soles. This wrong statement, according to Riecke, is due either to the lack of knowledge of the normal conditions or to the fact that the excretory ducts, being enclosed in thick horny cylinders, appear to be close together. The cornification of the sweat gland ducts begins at their mouths on the surface of the epidermis and is present throughout the epidermis. In a few ducts the cornification proceeds down into the derma for a variable distance. Moore and Warfield state that the glandular cells of both varieties of glands (sweat and sebaceous) are seen to be swollen in places and seem to be undergoing some sort of degeneration, but never cornification.

Concerning the sebaceous glands, there is also a wide diversity of opinion. Caspary [31] and Straube report total absence of sebaceous glands in their cases, while Wassmuth found them to be increased in

30. Carbone: Un caso di ictiosi congenita. Arch. per le sc. med., **15**:349, 1891.

31. Caspary: Ueber Ichthyosis fetalis. Vrtljschr. f. Dermat. **13**:3, 1886.

number. The walls of their ducts are cornified or the mouths of the ducts are occluded by horny plugs (Bruck). Rudimentary development or even total atrophy has been observed by Müller, Claus, Gerstenberg, Jahn, Schabel and Stühlinger. In some of these cases, however, besides completely degenerated glands, other completely normal glands were seen. Irregularities in the course of the excretory ducts in the form of cylindrical or spindle shaped dilatations or thickenings are mentioned most frequently. The ducts were found partly well formed, partly with cystlike dilatations, or atrophied and with their secretion scanty and mostly retained.

In the hair follicles and the hair, conditions were found to be similar to those present in the sebaceous glands. Their under development or atrophy was reported by Gerstenberg, Koller, Kyber and Wassmuth. Markedly elongated hair follicles with dilated lumen and abundant fat contents were observed by Claus, thickened hair follicles by v. Schab. By the excessive thickness of the epidermis the development of the hair and especially of lanugo hair is frequently retarded and the hairs remain coiled down in the hair follicles. Root sheaths were found totally or partially cornified by Claus. Riecke states that the hair papilla and the lower third of the hair follicle, including its content, are normally developed in almost all instances. Only in places of especially extensive horny deposits, many hairs in their lowermost portions give an impression of light atrophy.

The main site of the changes, which consists of superimposed horny lamellae, either loose or adherent, is the hair funnel, and these pathologic formations in most cases reach to the mouths of sebaceous glands only. The hair funnels filled with horny masses are in some places enlarged. Peculiar is the behavior of the hairs in the fissures which intervene between the horny plates. The hairs are always so situated that they exert traction against the horny shields surrounding the fissures. On transverse section of the fissures they appear to diverge in both directions. "In one piece of the skin which contained a fissure dividing in the shape of a fork, enclosing horny shields, there was an instructive alteration in the direction of the hair and of the papillae. In both fissures the divergence of the papillae and of the hairs was very striking. In the horny plate lying between, the convergence of the papillae and of the hairs towards the middle was noted. This picture gives us a clew as to the time of beginning of cornification, since the horny armor seems to determine the direction of all the hairs present. The stiffness of the surface therefore must have appeared during embryonal life at a time when the rudiments of the hairs of this location have all developed" (Riecke). Esoff [32] describes hyperplastic lateral epithelial outgrowths of the hair follicles.

32. Esoff: Beitrag zur Lehre von der Ichthyosis und von den Epithelialwuchrungen bei dersselben nebst Bemerkungen über den Haarwechsel, Virch. Arch. f. path. Anat. **69**:417, 1877.

In general the various regions of the skin differ only in the degree of the changes. The quantity of the hair determines the formation of horny shields, and the horny deposits in densely haired regions appear to be sievelike. In the horny shields of the regions of the body covered by lanugo hair the wavelike layers prevail and the horny canals for the hairs are arranged in groups.

The horny deposits of those portions of the skin that possess no hair have a great resemblance to callous horny masses. They contain neither systems of interspaces due to the hair taking part in the process, nor the above described enclosures of necrotic portions of the tissues, the change being chiefly simple hyperkeratosis.

Thus the skin of the soles and of the palms shows some structural differences from the skin in other portions of the body. Some of these differences have been mentioned already. Stratum corneum is formed of numerous superimposed layers of horny plates. Stratum lucidum is indicated and stratum granulosum easily demonstrable. Stratum germinativum is normal. The dermis is normal, the papillae being only slightly developed, however. The coils of the sweat glands are everywhere well developed and form at the border of the subcutaneous tissue an almost continuous layer; their excretory ducts are normal. There are no enclosures.

The nail plate on the fingers is covered by a thick layer of horny lamellae. The nail bed and the nail plate are normal.

Riecke summarizes the characteristic histologic findings as excessive formation and accumulation of horny cells, enormously increased cornification in the hair funnels, slightly altered papillae, separation of portions of the cutis and their enclosure within the stratum corneum. Brandweiner says that "in less severe cases there are no essential differences from the picture as presented in ordinary ichthyosis."

As to the development of the pathologic condition of the skin, the majority of authors are of the opinion that the leather-like epidermal covering, because of the lack of elasticity, has become too narrow for the growing fetus and cracked in many places. Thus a number of fissures are formed which, because of the favorable condition of the skin surrounded by amniotic fluid, gradually became covered by the skin again. By continued traction the flattened down margins develop and due to the same cause is also the peculiar course of the ducts of the sweat glands on the hands and feet (Müller, Bruck, Jahn, Straube, von Schab).

Wassmuth attempted to explain the process by deficient or lacking desquamation of the superficial layers of the stratum corneum, which again is due to the epidermis not reaching complete cornification.

Besides pathologic alterations of the skin and skin appendages, pathologic changes were found also in other organs of the body. Those that may probably be regarded as secondary to the skin changes seem to be pretty constant, e. g., congestion of the internal organs, while those alterations that must be regarded as primary changes and having probably some bearing on the etiology of the condition, are somewhat inconstant.

Congestion of the internal organs so extensive as to bring about a picture of exudative inflammation in some cases was observed by many authors (Firmin, Daniel and Cordes, Riecke, Wassmuth, Gerstenberg, Moore and Warfield). Firmin makes an interesting remark that this congestion is analogous to the one found in individuals dying of extensive burns. In the case studied by Daniel and Cordes the kidneys showed lesions of acute exudative nephritis, in the liver there was granular degeneration of the hepatic cells and the meninges of the brain showed extensive hemorrhage, while other organs presented no pathologic changes save intense congestion.

Winfield [33] found total absence of the thyroid gland. Moore and Warfield found atrophy of the thyroid gland and of the thymus. They described the thyroid gland as follows:

> Thyroid gland lies in the usual position and has an isthmus connecting the two lobes. The lateral lobes are about 13 mm. long, 6 mm. wide and 5 mm. thick. The gland is undoubtedly much smaller than normal, but in gross shows nothing striking, except the small size. It is, like all the organs, congested and at one spot there is a macroscopic hemorrhage within the gland.
>
> Interesting and curious changes are seen in the gland, which have robbed it of all resemblance to the normal thyroid. In the sections of a normal thyroid of an 8 months, 40 cm. fetus we found a delicate framework of connective tissue, and alveoli lined with low cuboidal cells and filled with homogenous colloid. Sections of the thyroid in our case show none of the normal appearances. A glance at the specimen under a low power shows cellular collections separated from each other by dense bands of fibrous tissue. No typical alveoli are seen, but here and there open spaces, irregular in shape, which contain cells and granular material, and which have very little resemblance to the normal colloid. A mixture of desquamated cells and granular material has replaced the colloid substance. Instead of the symmetrical, mosaic-like appearance that the normal alveoli filled with colloid give to the gland, there is confusion and conglomeration. The alveoli are lined for the most part by columnar cells, having a small, round, deeply staining nucleus near the bases of the cells. A large cell with a large vesicular nucleus is also seen among the other cells in the alveolar wall. Both kinds of cells go to make up the alveoli, and are also found free in the centers of the alveoli. These cells in many places are seen to have undergone partial degeneration. The material in the alveoli in which the cast off cells lie, is granular and does not give the homogenous stain of normal colloid. There is no lining layer of cells in the sense used in speaking of normal alveoli. The two kinds of cells described above, which predominate in the cellular tissue, are mixed together in no regular arrangement. Some of

33. Winfield: A Contribution to the Etiology of Congenital Ichthyosis; Report of a Case with Absence of the Thyroid, with Microscopic Report of the Condition of the Skin, J. Cutan. Dis. **15**:516, 1887.

these so-called alveoli have been made to assume bizarre shapes by the ingrowth of the connective tissue in the wall, forming papillary processes that project into the spaces.

There is an enormous increase in the connective tissue, which shows both hyalin degeneration and young fresh fibers as evidenced by the fibroblasts seen in portions of the section. The rapidly growing fibrous tissue seems to be compressing the gland and causing it to atrophy. The increase of fibrous tissue, in the main, is seen where the large lobulations of the gland are formed, although fairly large strands are seen separating the smaller lobules.

The blood vessels are distended with blood, and at one spot in the gland there is considerable hemorrhage, apparently having come from a ruptured vessel. There is also thickening of the media, and adventitia but no calcification or atheroma.

The appearance of the gland is quite like the atrophic thyroid in sporadic cretinism, as described by Packard and Hand.[34] They found thickened arterioles and calcareous degeneration. It is interesting that nowhere, so far as we can find, are such changes noted in the thyroid gland, except in the two conditions above, and that cretinism, keratosis fetalis, and fetal athyrosis of pigs (Smith [35]) are characterized by marked cutaneous changes. The coincidence is curious. Thyroid administration has been tried in the treatment of ichthyosis (Fox [36]), and Nordman and Badet [37] report the cure of a case of congenital variety by the administration of thyroid. In previously reported cases, the condition of the thyroid has received scant attention. Huebschmann [38] reported findings similar to those of Moore and Warfield. In the only other case of fetal ichthyosis where examination of the thyroid is specifically mentioned (Daniel and Cordes) it was said to be normal macroscopically and microscopically.

Lesions of congenital syphilis were never found in this condition. Gerstenberg, who regards keratosis diffusa fetalis as a trophoneurosis, found striking pictures of interstitial neuritis in the brachial plexus.

It is of considerable importance that, while most of the patients die even in the absence of complication, no pathologic changes were found that could be designated as the ultimate cause of death and the question as to what causes death in these cases has not yet been answered. It is certainly not inanition, because even those that were fed by catheter died. It seems rather to be due to deficiency in the

34. Packard and Hand: A Contribution to the Pathological Anatomy of Sporadic Cretinism, Am. J. M. Sc. **122**:289, 1901.

35. Smith: Fetal Athyrosis. A Study of the Iodin Requirements of the Pregnant Cow, J. Biol. Chem. **29**:226, 1917.

36. Fox: Ichthyosis in a Child Aged 16 Months, Treated by Thyroid Extract, Proc. Roy. Soc. Med., London **4**:72, 1910.

37. Nordman et Badet: Ichthyose congénitale, guérie par le traitment thyroidien, Loire méd. **29**:459, 1910.

38. Huebschmann: Ueber Ichthyosis congenita. Arb. a. d. Geb. d. path. Anat. u. Bakt., **6**:500, 1908.

function of the skin, to prematurity (which is the rule) and to deficient constitution. In a few cases which died shortly after birth pneumonia was present.

REPORT OF CASE

*Clinical History.*—The child was admitted to the Sarah Morris Hospital for Children when one day old. The external surface of the body showed the condition described in the necropsy report. Birth was normal, at the end of a normal full term pregnancy. The mother had had no miscarriages. Two previous children were normal. The mother has had eczema for many years. Her blood Wassermann was negative. The child was catheter fed with breast milk after admission, but appeared to be weak and had difficulty in swallowing. Death occured on the eighth day after birth.

*Necropsy Report* (abstract of report by Dr. I. Perlstein).—This is the body of an undersized child which is 43 cm. long and weighs 1,575 gm. The skin presents changes due to perverted keratinization. The integument is thickened and hardened, split up into plates and scales by rents and fissures of various depth and width (Fig. 1). The general color is grayish or yellowish. The skin is hard and leathery to touch. The epidermis plates are of various shape and size (Fig. 2). They are mostly angular. Some are round. They are smallest where the most movements occur, as in the groins, popliteal spaces, axillae, etc. They are largest on the scalp and on the back (Fig. 3). The hands and feet are edematous, small and covered by smooth glistening skin (Figs. 4 and 5). They are atrophic and the joints are ankylosed. The nails of hands and feet are poorly developed. The eyes are small, slitlike and deeply seated due to edema of the eyelids, which are also covered by horny plates. Eyelashes and eyebrows are not seen. No hair is to be seen anywhere upon the surface of the body except in the occipital region of the scalp, where a narrow fringe of fine, sparse, short, light colored hair is present. The mouth is open and gaping, and has the appearance of that of a fish (Fig. 6). It is surrounded by plates and rhagades which produce a contraction of the soft parts. The nose appears flat and small because the depressions around it are filled up by thickened skin. The auricles are not visible, since they are covered by epidermic plates which also occlude the external auricular meatus. The external genitals are small and covered by epidermis plates.

The body is opened by the usual longitudinal incision. There is a very thin subcutaneous layer of fat. The peritoneal and thoracic cavities have smooth and glistening serous surfaces and contain the usual amount of moisture. The thoracic and abdominal organs are in normal relation to each other. They are removed in toto including the tongue and organs of the neck.

The internal organs, except the lungs, show nothing of note except congestion. The right lung weighs 40 grams and is covered in places by a small amount of fibrin. The upper lobe is completely consolidated and the two lower lobes are consolidated in the posterior portions. These parts are dark red and fleshy in color and sink in water. Left lung: The upper lobe has a small dark red, hard patch which measures 2 cm. in diameter, the lower lobe has three areas of the same kind, which are somewhat smaller. The testes and glands of internal secretion are normal, with the exception of the thyroid. The latter nearly encircles the trachea. It has a right and left lobe connected by a thick isthmus. It weighs 5 gm. The left lobe measures 2 x 1.3 x 1 cm.; the right, 1.8 x 1.1 x 1 cm. The isthmus measures 0.7 cm. between lobes, 1 cm. from superior to inferior margin, and 3 mm. in thickness. The left thyroid at its upper posterior pole, at the junction with the isthmus, contains just beneath the capsule two pale areas each 5 mm. x 3 mm., separated from each other by a very narrow strip of darker tissue. The right lobe at the same situation contains an area of similar tissue. At the middle of the outer lateral aspect of the left thyroid is a pale subcapsular area 2 mm. in diameter.

Anatomic diagnosis: Congenital hyperkeratosis; acute lobar pneumonia.

MICROSCOPIC EXAMINATION

With the exception of the lungs, thyroid and skin, the microscopic examination shows nothing, except extreme congestion.

Lung: In the unconsolidated portion of the lung tissue the alveoli vary in size. The septums are thick and contain many oval, rather deeply stained nuclei, together with a few lymphocytes. Some of the smaller alveoli are completely filled by swollen, desquamated epithelium. In the consolidated tissue, which is rather sharply delimited from that which contains air, the original lung structure is recognizable with difficulty. Many alveoli are densely filled with red blood corpuscles. Other areas are more cellular, the alveoli being packed with desquamated epithelia, lymphocytes and pus cells. While polynuclear leukocytes are numerous in places, in general the lymphocyte is the predominating cell type. In the consolidated tissue are several clumps of bacteria, some definitely within small blood vessels.

Thyroid: In sections including the entire right lobe, the thyroid nature of the tissue is nonrecognizable except in a small narrow subcapsular zone. The rest of the tissue is subdivided into lobules of varying size by bands of fibrous tissue of varying thickness (Fig. 7). The stroma carries numerous blood vessels which are markedly distended with blood. The lobules are composed of closely placed round and oval cells which show no follicular arrangement and no lumen formation. In their appearance the lobules suggest lymphoid rather than thyroid tissue. The cells have nuclei which vary in size from that of the nucleus of a small lymphocyte to that of a large unripe lymphocyte. The small nuclei are dense and deeply stained, the larger ones somewhat more vesicular. The nucleus is surrounded by a relatively large amount of homogenous eosin stained cytoplasm. The larger cells measure up to 18 microns in diameter and have nuclei up to 10 microns in diameter. The smaller cells average 13 microns and have nuclei 6.6 microns in diameter. In a relatively small subcapsular area of thyroid tissue, follicles are present in the lobules (Fig. 8). The follicles vary in diameter from 70 to 220 microns, only a few being of the latter size, the average about 100 microns in diameter. The follicles are lined by a single layer of low cuboidal epithelium, with nuclei small and condensed and of the same size and appearance as the smaller nuclei in those portions of the gland where no follicles are present. The lumens of the follicles contain deeply eosin stained, normal appearing colloid. The surface area of the entire section is 80 sq. mm.; that of the differentiated area 13.5 sq. mm. The pale areas noted in the gross description of the left lobe are similar small islands of differentiated thyroid tissue. Only in the four small areas noted, namely at the upper poles of the two lobes, and on the lateral aspect of the left lobe, does the thyroid show its normally differentiated structure and in these areas only the most superficial subcapsular zone is differentiated.

Skin: Sections were taken from the back, the abdomen and the scalp, where the keratosis was very marked; from the leg, where the thickening was only slight; from the sole of the foot in an area which showed no macroscopic keratosis; from the thin smooth skin of the great toe; from the margin of the eyelid and from the lip.

Skin of the back: The section includes one of the broader furrows with some of the markedly thickened skin on each side. In the latter situation the free surface is covered by a markedly thick, horny layer, most of which is in finely laminated, whorllike areas, the majority of which have a clear space or opening in the center. A few groups of small compressed and condensed nuclei are scattered about in the horny material, usually in that which lies between the whorls. The upper surface of the epidermis itself is very irregular, projections caused by broad, flat topped papillary structures alternating with depressed areas of about the same width. The projections are formed by three to as many as eight slender, long, dermal papillae covered by and separated from each other by epidermis (Fig. 9). In the depressed areas between the

projections the papillae are short and thick. The epidermis is very thin. The lowermost cells are cuboidal and are not so high or so regularly arranged as the normal malpighian layer. Above this is a layer which is from two to four cells thick over the summits of the papillae (Fig. 10) and which appears to correspond to the stratum spinosum. The cells, however, are very closely placed and show no intercellular bridges. Above this is a layer of about equal thickness, the nuclei of which are slightly more widely separated and lie in a dense, deeply eosin stained matrix. This layer appears to correspond to the stratum granulosum, but individual cell outlines are not distinguishable and the layer contains no granules except in a few small widely separated areas. Above this comes a nonnucleated layer about equal in thickness to the rest of the epidermis, composed of very thin lamellae arranged parallel to the surface of the epidermis. The deeper half of this area takes a purple tinge, due to the presence of numerous very minute blue staining granules and corresponds apparently to the stratum lucidum. The superficial half of this zone is free of granules, has the appearance of closely laminated stratum corneum, and goes over superficially into the thick whorl-like horny material described.

The cutis vera contains many spindle nuclei and a few lymphocytes. Hair follicles in the deeper cutis are few in number and widely separated, but just beneath the epidermis they are more numerous. These superficial follicles do not extend down much below the level of the deepest portion of the interpapillary epithelial down growths of the epidermis, their diameter is two to several times greater than normal, and they appear to take part in bringing about the irregularity of the epidermis. The widely separated follicles in the deeper tissue are smaller in diameter. Hornified material extends down into the hair funnels and into the follicles, the change being present even in the smaller deeper follicles, each of which contains a hyalin, homogenous, deeply eosin stained center, which at its middle point contains a small clear area. In most of the follicles a few cells of the stratum granulosum type are present. No normal sebaceous glands are seen, but about an occasional deep follicle are one to three atrophic compressed glandlike structures which look more like sweat glands than like sebaceous glands. Normal coiled sweat glands are also absent, but straight cellular strands, apparently compressed sweat ducts, lie widely separated in the cutis. The direction of these and of the hairs is such that they make a very acute angle with the epidermis, often running almost parallel to the latter in their course through the cutis. The blood vessels of the papillae and of the rest of the skin are markedly engorged. In the deeper layer of the cutis, just above the thin layer of fetal, not fully differentiated subcutaneous fat, the connective tissue bundles are widely separated by clear spaces of varying size, evidently the result of edema.

In the furrow the very thick whorllike horny layer is absent (Fig. 11). The epidermis here is covered by a thin horny layer about equal in thickness to that at the sides of the furrow. The epidermis, which here does not show the papilla-like irregularity of the thicker skin, is atrophic. The papillae are widely separated and they are very short and blunt. The normal stratification of the epidermis is not apparent. Above the cellular layer, corresponding apparently to the stratum spinosum, is a laminated layer which contains small, slender, compressed, very deeply stained nuclei lying in a hyalin matrix. Above this in turn is the horny layer. The tissue immediately beneath the epidermis contains many young connective tissue nuclei and a few lymphocytes and the blood vessels are markedly distended. Deeper down the stroma is edematous. Hair follicles are fewer in number than in the neighboring thickened skin and no sebaceous glands are recognizable. The sweat glands have the same atrophic appearance as those beneath the thickened skin.

The walls of the larger arteries and veins show no abnormality and the nerve trunks present also appear normal.

The skin of the abdomen shows the same condition as that of the back. In skin from the leg the same changes are present, but hair follicles are more numerous and the whorllike horny layer is not so thick as on the back. The hair follicles are here, as elsewhere, centrally hornified.

Scalp: In sections of the scalp taken from that portion which showed in the gross a fine growth of hair, the epidermis with its markedly hypertrophied whorled horny layer is three to four mm. thick. The epidermis has lost almost entirely its cellular character and has been transformed into keratohyalin lamellae. The stratum malpighii consists of an incomplete layer of cuboidal cells with small, deeply stained nuclei. In many places these cells constitute the only epidermal cellular elements left. In other places, there are superficially to this layer, a few cells, in general of the stratum spinosum type but without prickles and with nuclei which stain faintly, some of which appear edematous, others of which appear to have lost both fluid and chromatin. The papillae are very long and slender (Fig. 12) and they are arranged in groups of two or more, so that the upper surface of the epidermis has the irregular papillary character noted in the skin elsewhere. The stroma of the papillae is so edematous that it has the structure of mucoid connective tissue. In the latter lie blood filled small vessels and larger empty endothelial lined spaces, the latter apparently lymphatics. The hair follicles which here are fairly numerous are cut tangentially and transversely, indicating their oblique course through the tissue. Lying beside some of the follicles are atrophic sebaceous glands. Almost every follicle is accompanied by a well developed bundle of muscle. Sweat glands are very few in number, widely separated and atrophic.

Skin of the Sole: Of the skin from various areas examined, that of the sole of the foot is nearest normal. The horny layer, while about twice the thickness of the rest of the epidermis and its papillae, does not show the whorllike arrangement which is so striking elsewhere. Its closely placed lamellae are regularly arranged, run parallel to the surface of the epidermis and contain a slight amount of finely granular blue stained material. Granulosum and lucidum layers are not present, the stratum spinosum going over directly into a layer from five to eight cells thick, in which the nuclei are small and condensed and the cytoplasm dense, hyalin and without extranuclear chromatin. This layer goes over sharply into the stratum corneum, which contains no nuclei but does contain, as already noted, scattered fine chromatin dust. The papillae are long, slender and closely placed. Just beneath the papillae the stroma contains many spindle nuclei and a few lymphocytes. Sweat glands are numerous, closely placed and normal in appearance. Their ducts, cut obliquely and transversely, form numerous cellular strands and islands in the stroma beneath the epidermis. No hair follicles or sebaceous glands are present. The thin glistening skin of the toe has the same structure as that of the sole except that the papillae are not so long, slender and closely placed and the numerous sweat glands and ducts are absent.

In order to determine whether the changes described are limited to the covering epidermis, sections were taken from areas other than the skin which normally are covered by squamous epithelium and from places where the epidermis goes over into nonhornified epithelium. The squamous epithelium of the upper esophagus is normal. That of the tongue likewise shows none of the changes noted in the epidermis. Just at the tip of the tongue a thin superficial layer of the epithelium is more hyalin than normal and its nuclei are condensed. This change is apparently due to drying, the result of the constantly open condition of the mouth. The papillae at the tip of the tongue contain many young fibroblast nuclei and the vessels are engorged. The deeper structures show no abnormality. The epidermis of the outer surface of the eyelid shows the same hyperkeratosis and the same hornification of hair follicles as the rest of the epidermis, the atrophy and irregularity of the epidermis itself are not so marked, and normal sebaceous glands are more numerous here than elsewhere. At the lower margin of the eyelid the hypertrophied horny layer

ceases very abruptly. The epidermis here is thin. On the inner surface of the lid the squamous epithelium is desquamated in numerous small areas. In a section through the lower lip the epidermis is more nearly normal than elsewhere. All the normal epidermal layers are distinguishable here, a condition not noted in skin from any other area examined. Many of the cells of the prickle layer are vacuolated. The surface is covered by a thin horny layer whose lamellae, which run parallel to the surface, contain a few shrunken compressed nuclei. The hair follicles are long, run at right angles to the surface, are centrally hyalinized and each has a normal sebaceous gland. The hair containing skin of the lip goes over very sharply into the hair-free epidermis of the scarlet portion of the lip. The latter appears normal. It is covered by a thin regular stratum corneum.

Elastic tissue of the skin: Sections from different areas were stained with Verhoeff's elastic tissue stain. The skin of the foot, which in the hematoxylin and eosin stain preparations shows little deviation from the normal, except moderate epidermal hypertrophy, contains many elastic fibrils arranged in the normal manner. In situations where the horny layer is markedly thickened and the epidermis atrophied, the elastic fibrils have largely disappeared. Those elements which can still be recognized occur as short, markedly tortuous and in places swollen fibrils and as rows of fine granules. In the deep subcutaneous tissue just above the muscle the elastic fibers are normally preserved. Where the skin is markedly furrowed, the elastic tissue shows very interesting relationships. At the margins of the furrows beneath the thickened skin the fibrils are absent or degenerated as described, whereas beneath the furrow, which is covered by a relatively thin regular horny layer, the elastic tissue is larger in amount and more normal in arrangement and appearance.

No treponemas are seen in sections of the various tissues and organs prepared by the Levaditi method. The placenta and umbilical cord are normal microscopically and contain no treponemas in Levaditi preparations.

## DISCUSSION

The pathology of the skin has been given in detail, because from the study of the changes in this typical and marked case, conclusions have been reached in regard to the pathogenesis of the hyperkeratotic condition which are somewhat at variance with those of previous writers.

Bossert considers the condition one of abnormal hornification of hair follicles and skin, associated with abnormality in the course of the hairs. The latter he appears to regard a fundamental condition. Meyenburg finds thickening of the horny layer to be the one constant feature in all descriptions of the process, changes in the cellular epidermis being less uniformly noted. In his case there was no hair anlage, hence Bossert's idea of the importance of hornification of hair funnels and obliquity of hairs does not appear to hold. The oblique course of the sebaceous gland ducts in his case Meyenburg holds to have been brought about mechanically by tension of the elastic fibrils at the bottoms of the fissures. Schabel and Stühlinger believe that incomplete transformation of the epithelial cells of the sebaceous glands into fat prevents the normal formation of vernix caseosa. The incompletely transformed materials are retained and lead to the formation

of horny plates and shields. Wassmuth considers deficient desquamation, due to incomplete and abnormal hornification, the essential factor. Riecke concludes that the process is one of excessive formation and accumulation of horny cells, a conclusion which Esoff had reached many years previously, but he offers no explanation of how this process is brought about. He excludes the formative part of the skin from any part in the process, stating that the changes in the deeper epidermal layers lie within the limit of normal and that the process has no effect on the production of papillae. That Gerstenberg considers the process a trophoneurosis has been mentioned. Moore and Warfield suggest that absence of the thyroid, noted in their case, may be a factor in the persistence of the epitrichial layer of the epidermis. Unna places the condition among the stagmatory tumors due to progressive disturbance of nutrition, under the malformations of the skin. He defines it as a congenital excessive firmness of the whole horny layer, whose essential feature is a firmer connection of the epithelium. Papillarly changes he holds to be secondary to the influence of the hyperkeratosis on the rapidly proliferating embryonic prickle layer.

In the case here described the abnormal development of the horny layer, which is the most striking feature of the condition, is marked, and the hairs and the excretory ducts of the sweat glands take the very oblique course noted by others. But there are in addition other changes which are considered more fundamental. The absence of granulosum and lucidum layers in the epidermis indicates that the condition is not simply one of abnormal cornification, but that there is at work some interference with that process which normally transforms the epidermal cells of the deepest layer into the horny scales of the superficial layer through a definite and regular sequence of changes. Associated with the alterations in the epidermis itself are hypertrophy of the dermal papillae in most situations, a condition especially marked in the scalp where hyperplasia of the horny layer is extreme, and atrophy of papillae in other areas. The cutis throughout is the seat of slight subacute inflammatory reaction, as is indicated by the presence of moderate numbers of lymphocytes and by the increase in young spindle nuclei. Hair follicles in general are much less numerous than normal and all show central cornification. Sebaceous glands are absent, or where present they are undergoing atrophy. The sweat glands are decreased in number, except in the skin of the sole, and those present are compressed or are undergoing atrophy.

It is inconceivable that the very thick stratum corneum which is present could be the result merely of abnormal hornification or of failure of normal desquamation during fetal life. Such an amount of

horny material could not be formed except from pre-existing epidermal cells. The latter could not be formed in numbers sufficient to produce such a thick stratum corneum unless there had been a previous stage of epidermal hypertrophy and hyperplasia. Evidences of such hypertrophy are present in the skin examined. In the sole of the foot, where hyperkeratosis is slight, the papillae are long, numerous and closely placed, and sweat glands are numerous. Where hyperkeratosis is most marked many of the papillae are still abnormally long, while others are short and atrophic. The interpretation of the changes noted in this case is that the primary condition was one of hypertrophy of the skin and that the hypertrophy led to an increase in the stratum corneum. Hypertrophy was followed by atrophy, a condition evidenced by the thinning of the cellular portion of the epidermis and by the disappearance of stratum granulosum and stratum lucidum; by flattening and loss of dermal papillae; by disappearance of hair follicles, sebaceous glands, and sweat glands, and by disappearance of elastic tissue.

The fissuring of the epidermis, the obliquity of the hairs and skin glands, and the deformity of the face and of the terminal phalanges of the fingers and toes are changes secondary to the atrophy. Irregularity in the disappearance of the elastic tissue during the stage of atrophy leads to irregular contraction of the skin, with the formation of fissures. At the same time, it leads to more or less general retraction of the skin, so that the phalanges become permanently flexed, deformed, and hindered in their further development. The oblique course of the hairs and of the skin glands is likewise due to this dislocation of the skin and appears to be purely mechanical.

The explanation of the causation of the series of changes described is another and more difficult matter. Because of the alterations which occur in the skin in conditions of loss of thyroid function, it would seem pertinent to consider the possibility of relationship of abnormality of thyroid function to keratosis diffusa fetalis. Absence of or failure of development of the thyroid has been noted by Winfield and by Moore and Warfield. In Wassmuth's case the parents were high-grade cretins. In Moore and Warfield's case the thymus was atrophic and fibrous. In our case the thymus shows no striking deviation from normal, except richness in Hassall's corpuscles, but the thyroid gives definite morphologic evidence of loss or absence of function. With the exception of four small, and relatively insignificant areas, the thyroid is totally undifferentiated. It is composed of small cells without any follicular arrangement and with no formation of secretory material, except in the small islands noted. In general, the abnormality of the thyroid in this case appears to be of the same nature as that

noted by Moore and Warfield in their case. (Compare their Figure 4 with our Figure 7.) Unfortunately, their illustrations are not accompanied by legends or by direct references in the text, so that it is impossible to decide whether their Figure 5 is an illustration of normal fetal thyroid which they studied or part of the thyroid from their case of keratosis fetalis. If the latter is the case their Figure 5 would be duplicated by our Figure 8, from one of the small differentiated areas of thyroid tissue. The condition of the thyroid is striking and suggestive, but thyroid deficiency cannot be considered an essential factor in keratosis diffusa fetalis unless it occurs more frequently or more uniformly than the previous literature indicates. None of the other glands of internal secretion showed any deviation from normal which might be held to have any relation to the general condition.

## SUMMARY

The case reported is an extreme and typical example of the condition under consideration. Thickening of the horny layer is marked. The hyperkeratosis is limited to those portions of the skin which normally develop a stratum corneum, and ceases sharply at those situations where the normal stratified horny epithelium goes over into nonhornified epithelium.

Associated with the abnormal keratinization are obliquity of the course of the hair follicles and of the skin glands, fissuring of the epidermis, and deformities and failures of development of the phlanges and of the face.

Evidences of papillary hypertrophy are present. The condition is considered to be primarily one of skin hypertrophy, which leads to an increased formation of epidermal horny material.

In the fully developed condition, atrophy of the skin is more prominent than hypertrophy, except in so far as the horny layer is concerned. The dermal papillae become shorter, flatter and less closely placed. Hairs, sebaceous glands, and sweat glands disappear, and there is a decrease in elastic tissue, the latter element remaining present in largest amount beneath the fissured areas.

The fissuring of the epidermis and the deformities of the extremities and other portions of the body are held to be secondary to the atrophic changes, being brought about by retraction of the skin.

With the exception of the thyroid and the lungs, the internal organs are negative, except for the marked congestion present.

The thyroid is undifferentiated and morphologically nonfunctioning. Deficient thyroid function during the developmental period may be a factor in the condition.

The condition has reached such an extreme degree of development by the time of birth as has been found to be incompatible with life in other cases. In this case pneumonia was the immediate cause of death.

## CONCLUSIONS

For the condition reported in the literature under the name ichthyosis congenita and a variety of other terms, which are based on some superficial gross anatomic peculiarity of the skin, the designation keratosis diffusa fetalis, based on the pathologic condition common to all the cases, is proposed.

The reported cases fall into three groups. In the first, to which the case here reported belongs, the abnormality is so extreme at birth as to be incompatible with a duration of life of more than a few days. In the second group, keratosis diffusa fetalis mitior, the condition is present at birth, but is not developed to so extreme a degree as in the first group. The duration of life depends on the rate at which the condition develops after birth and on the degree to which it develops. In the third group, keratosis diffusa fetalis tarda, evidences of the skin anomaly may not be present at birth. They develop after a period of variable length, and the degree of development which they reach is also variable.

Keratosis diffusa fetalis is a condition, having its origin in the fetal period of development, the most striking feature of which is marked increase in the horny layer of the epidermis and abnormal hornification of the epithelial skin structures.

The hyperkeratosis, which becomes the predominating element in the pathologic process, is believed to be the result of a preceding stage of hypertrophy and hyperplasia of the skin.

Absence of the thyroid or deficiency of thyroid function during intrauterine life may be a factor in the causation of the epidermal changes which characterize keratosis fetalis.[39]

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39. The following references may also be consulted:

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# STUDIES ON THE INORGANIC CONSTITUENTS OF MILK*

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## I. CHLORIDS IN HUMAN MILK

In discussions of the composition of human milk and of modifications of cow's milk, much stress is laid on the absolute and relative proportions of fats, carbohydrates and protein, but, as a rule, no mention is made of the concentration of the mineral constituents. As an example, we may cite the fact that in many clinics the most premature infant is given mixtures of whey, which may provide certain advantages in regard to the quality of the protein, but which contain 300 per cent. more chlorids than does human milk. A similar relation exists in connection with several of the other inorganic constituents.

This practice is, of course, based on the assumption that an excess of inorganic material is present even in human milk, and that this excess is not injurious, an assumption not based on experimental evidence. Theoretically, it is, of course, perfectly conceivable that such an excess of salts may not only increase the work of the kidneys to a dangerous degree, but may even induce intestinal disturbances.

Stimulated by recent work which has demonstrated the importance of the mineral elements of the diet, we began about one year ago a study of the mineral constituents of human milk and of the various modifications of cow's milk ordinarily used in infant feeding.

In this paper, which is the first of a series dealing with this subject, we shall consider only findings on the chlorids of human milk.

### METHOD OF ANALYSIS

Before attempting the collection of data, it was first necessary to find an analytical method by means of which it would be possible to obtain accurate results with a moderate outlay of time, and with relatively small amounts of material. Most of the milk chlorid determinations recorded in the literature were made either by gravimetric methods, usually from the weight of silver chlorid, or by the Volhard titration. In either case, a considerable volume of milk had to be evaporated to dryness, ashed in a platinum dish at low heat with the

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* From the Children's Medical Department and the Clinical Laboratory of the Massachusetts General Hospital.

help of an alkaline fusion mixture, and the ash then extracted with water. Such a process was tedious and time consuming, and one requiring an elaborate equipment and considerable chemical experience. The micro methods, which during the past ten years have been applied so extensively to the chemical study of the blood, can be used, in many cases, with slight modifications for the examination of milk.

Two methods for the determination of chlorids in blood are in current use, namely, Rappelye's [1] modification of the Volhard titration, and the iodonitric titration of McLean and Van Slyke.[2]

An attempt to utilize Rappelye's modified Volhard titration was unsuccessful because we were unable by means of it to obtain complete precipitations of the milk protein. We, therefore, have made use of the McLean-Van Slyke technic, with a few modifications made necessary by the nature of our problem.

Attempts to employ the Van Slyke-Donleavy [3] modifications, which involve the use of picric acid as a protein precipitant in place of the magnesium sulphate-acetic acid mixture of the original method, were unsuccessful, as it was found impossible also to obtain complete precipitation of the milk proteins in human milk by this technic. It was found, however, that if the proteins were first precipitated by means of a saturated solution of picric acid containing a little acetic acid and the acid silver nitrate solution then added without preliminary filtration, a clear filtrate could almost invariably be obtained.

In view of the fact that human milk contains only one-tenth as much chlorin as blood, it was necessary to make a few changes in the quantity and concentrations of the reagents. Although no claim for originality is made in this connection, it has seemed wise to furnish a brief description of our technic.

The titration as used by us, is as follows: To 3 c.c. of human milk contained in a 100 c.c. Erlenmeyer flask is added 9 c.c. of a 1.2 per cent. solution of picric acid containing 2 c.c. of glacial acetic acid per liter. After the mixture has stood for five minutes, 3 c.c. of the standard nitrate-nitric acid solution is added. After ten minutes the liquid is poured on a chlorid free filter. To 10 c.c. of the clear filtrate is added 2 c.c. of the starch indicator, and the excess of silver is then titrated by means of standard potassium iodid solution.

As it seemed best in this work to express our results in terms of milligrams of chlorin per 100 c.c. of milk, we have, in order to avoid the use of a factor, made a slight change in the concentrations of the

1. Rappelye, W. C.: J. Biol. Chem. **25**:509, 1918.
2. McLean, F. C., and Van Slyke, D. D.: J. Am. Chem. Soc. **37**:1128, 1915.
3. Van Slyke, D. D., and Donleavy, J. J.: J. Biol. Chem. **37**:551, 1919.

standard silver nitrate and standard potassium iodid solutions prescribed by McLean and Van Slyke.

SOLUTION 1

| | | |
|---|---|---|
| Silver nitrate | 4.780 | gm. |
| Nitric acid, sp. gr., 1.42 | 250. | c.c. |
| Distilled water, add to | 1,000 | c.c. |

One c.c. of this solution is equivalent to 1 mg. chlorin.

SOLUTION 2

| | | |
|---|---|---|
| Potassium iodid | 1.5 | gm. |
| Water, add to | 1,000. | c.c. |

This solution is standardized against the silver nitrate and so diluted that 20 c.c. are equivalent to 5 c c. of the silver solution.

SOLUTION 3

This consists of a solution of starch, sodium citrate and sodium nitrate made up according to the directions of Van Slyke and Donleavy.

It has recently been shown by Austin and Van Slyke [4] that the Van Slyke-Donleavy procedure, when used on whole blood, gives results greatly in excess of the truth. To remedy this they suggest the preliminary precipitation of proteins by means of picric acid, and the removal of the precipitate so obtained before the addition of the standard silver nitrate solution. Although our work on the subject had been concluded before the publication of this paper, we have made a few determinations by this method, and have, by means of it, obtained results essentially similar to those obtained by the technic described above.

TABLE 1.—COMPARISON OF RESULTS OBTAINED BY COAGULATION AND BY FUSION METHODS

| Sample | Source | Mg. Chlorin by Coagulation | Per 100 C.c. Milk by Fusion |
|---|---|---|---|
| 1 | Human | 75 | 77 |
| 2 | Human | 81 | 82 |
| 3 | Human | 32 | 35 |
| 4 | Human | 47 | 47 |
| 5 | Goat | 165 | 165 |

The corrections of our results have also been checked by means of Volhard titration used after the removal of the organic material by means of fusion with sodium carbonate.[5] In Table 1 a comparison of the results of determinations of the chlorin content of six samples of milk made by coagulation and fusion methods is shown.

4. Austin, J. H., and Van Slyke, D. D.: J. Biol. Chem. **41**:345, 1920.
5. Bull. 107 (revised), U. S. Dept. Agriculture.

### METHOD OF COLLECTION OF SPECIMENS

The specimens were collected by expressing the milk manually from the nipple into specially washed bottles. A breast pump was used in some instances, and it was found that the mechanical stimulation produced by this process caused no change in the chlorin content of the secretion. The nipples were carefully washed with water before collections were made and the use of boric acid and similar solutions was avoided.

The specimens were obtained in most instances about three minutes after the beginning of nursing, when the flow of milk had been established.

TABLE 2.—SHOWING CHLORIN CONTENT OF "FORE" AND "AFTER" MILK FROM NORMAL WOMEN

| Number | Mg. Chlorin in "Fore" Milk | Mg. Chlorin in "After" Milk | Period of Lactation, Weeks |
|---|---|---|---|
| 21–22 | 53.0 | 64.0 | 1 |
| 23–24 | 92.0 | 61.0 | 1 |
| 25–26 | 25.9 | 34.0 | 2 |
| 27–28 | 48.3 | 32.7 | 1 |
| 29–30 | 71.0 | 74.5 | 1 |
| 31–32 | 14.1 | 42.0 | 2 |
| 33–34 | 43.0 | 34.0 | 2 |
| 35–36 | 107.0 | 96.6 | 1 |
| 45–46 | 59.0 | 50.0 | 7 |
| 52–53 | 93.0 | 10.2 | 7 |
| 62–63 | 72.0 | 10.2 | 2 |
| 86–87 | 40.0 | 54.0 | 30 |
| 102–103 | 76.5 | 40.6 | 1 |
| 127–128 | 42.0 | 42.0 | 3 |
| 316–317 | 40.8 | 36.0 | 9 |
| 318–319 | 36.0 | 35.0 | 9 |
| 320–321 | 37.8 | 37.8 | 9 |
| 322–323 | 41.4 | 38.4 | 9 |
| 312–313 | 29.4 | 30.0 | 52 |
| 314–315 | 36.0 | 28.8 | 52 |
| 177–178 | 22.9 | 29.8 | 17 |
| 168–169 | 75.0 | 87.0 | 3 |
| 149–150 | 48.0 | 54.0 | 11 |
| 143–144 | 51.0 | 51.0 | 32 |
| 127–128 | 42.0 | 42.0 | 3 |
| 125–126 | 42.0 | 47.0 | 3 |
| 14–15 | 28.2 | 24.6 | 10 |

This method was adopted as larger specimens were obtained with less difficulty, and was used only after we had satisfied ourselves that no constant differences were noted in the "fore" and "after" milk, as can be seen from Table 2. The specimens used in this table were obtained from women who had large amounts of milk.

### SOURCE OF MATERIAL

The specimens of milk were obtained from various sources, namely, from the Outpatient Department of the Massachusetts General Hospital, the Boston Lying-In Hospital, the Clinics of the Boston Baby Hygiene Association, the Boston Wet Nurse Directory, and from private patients.

In Table 3 we have arranged, according to the period of lactation, the results obtained on all the 327 samples of milk examined. In many instances, the results represent averages of as many as ten specimens collected from one woman. Figure 1 shows a curve of the average concentration of chlorin and the maximum variation for each week as based on the results in Table 3.

TABLE 3.—AVERAGE OF RESULTS ON DETERMINATION OF CHLORIN IN 327 SPECIMENS OF HUMAN MILK TAKEN FROM THE FIRST TO THE SEVENTY-FOURTH WEEK OF LACTATION

| Mg. Chlorin per 100 C.c. of Milk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1st Wk. | 2d Wk. | 3d Wk. | 4th Wk. | 5th Wk. | 6th Wk. | 7th Wk. | 8th Wk. | 9th Wk. | 10th Wk. | 11th Wk. | 12th Wk. | 13th Wk. | 15th Wk. | 16th Wk. | 17th Wk. | 18th Wk. |
| 120.0 | 30.0 | 49.0 | 73.5 | 21.9 | 64.5 | 54.3 | 36.2 | 44.7 | 50.0 | 31.0 | 48.0 | 96.0 | 112.0 | 71.0 | 60.0 | 75.0 |
| 81.5 | 28.0 | 39.7 | 86.0 | 49.0 | | 71.9 | | 49.2 | 26.9 | 43.3 | | 73.8 | 45.7 | 105.0 | 111.0 | 40.8 |
| 36.0 | 41.0 | 36.0 | 69.0 | 39.0 | | 36.0 | | 60.8 | 52.0 | 51.0 | | 60.0 | 43.8 | | 47.0 | |
| 81.0 | 114.0 | 37.2 | 30.0 | 43.5 | | 39.0 | | 38.0 | | 61.5 | | 42.0 | | | 28.3 | |
| 61.0 | 117.0 | 97.0 | 72.8 | 31.0 | | 45.0 | | | | | | | | | 33.0 | |
| 111.0 | 111.0 | 94.0 | 77.7 | | | | | | | | | | | | 34.0 | |
| 51.0 | 111.0 | 44.5 | 82.0 | | | | | | | | | | | | | |
| 46.5 | 99.0 | 42.0 | 36.0 | | | | | | | | | | | | | |
| 58.5 | 60.0 | 42.0 | | | | | | | | | | | | | | |
| 61.0 | 87.0 | 81.0 | | | | | | | | | | | | | | |
| 40.5 | 38.9 | 52.0 | | | | | | | | | | | | | | |
| 72.7 | 75.0 | 55.1 | | | | | | | | | | | | | | |
| 101.8 | 49.8 | 40.6 | | | | | | | | | | | | | | |
| 75.0 | 58.6 | | | | | | | | | | | | | | | |
| 111.4 | 102.3 | | | | | | | | | | | | | | | |
| 42.0 | 65.0 | | | | | | | | | | | | | | | |
| 158.3 | 56.0 | | | | | | | | | | | | | | | |
| 78.0 | 50.6 | | | | | | | | | | | | | | | |
| | 60.0 | | | | | | | | | | | | | | | |

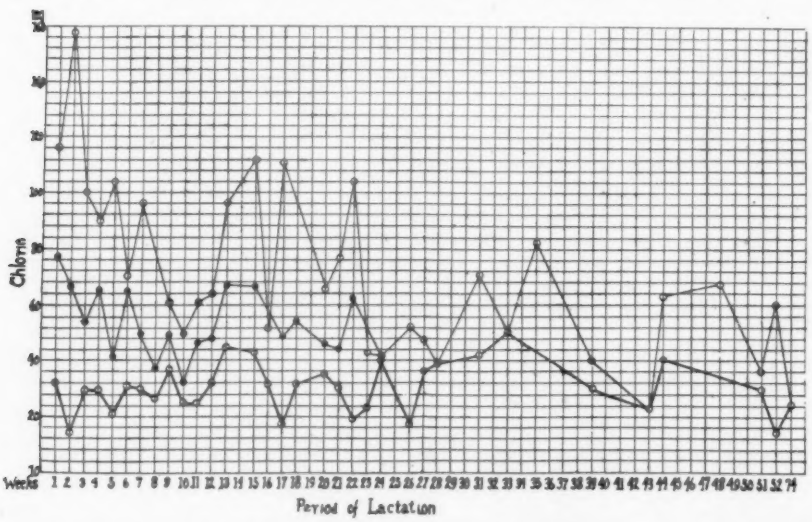
| 20th Wk. | 21st Wk. | 22d Wk. | 23d Wk. | 24th Wk. | 26th Wk. | 28th Wk. | 29th Wk. | 34th Wk. | 39th Wk. | 43d Wk. | 47th Wk. | 48th Wk. | 51st Wk. | 52d Wk. | 74th Wk. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 38.2 | 30.0 | 43.5 | 72.5 | 43.8 | 19.5 | 38.4 | 53.6 | 82.8 | 36.6 | 23.4 | 67.0 | 49.2 | 31.0 | 60.0 | 34.8 |
| 47.3 | 66.0 | 106.0 | 24.0 | | 52.2 | | 56.7 | 73.8 | | | | | | 18.0 | |
| 45.4 | 40.2 | 24.9 | | | | | | | | | | | | 35.6 | |
| 54.0 | 42.0 | 41.1 | | | | | | | | | | | | | |
| | | 101.3 | | | | | | | | | | | | | |

The results presented in Table 3 show that our average after the first two weeks of lactation is 52.6 mg. chlorin per 100 c.c. of milk. The average, if all periods of lactation are considered, is 58.2. This approaches the average results to be found in the literature as completed by Holt, Courtney and Fales.[6] As has been noted formerly, there is a tendency toward slightly high concentration of chlorin to occur during the first week, as shown in the accompanying illustration, after which the average remains about constant up to the seventeenth month.

Extreme variations were noted in the chlorin content of specimens from women in the same period of lactation and in specimens collected from individuals during a single day. Table 3 and the second curve in the illustration are based on averages, and show, in a measure, only the

6. Holt, L. E.; Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. **10**: 229 (Oct.) 1915.

frequency and the degree of these variations. In some instances, there was more than 300 per cent. difference in the chlorin content in individual specimens taken from one woman during twenty-four hours, more than 1,000 per cent. in specimens from different women at the same period of lactation. Figures as low as 14.1 mg. and as high as 156.8 have been obtained. This extreme variation may be accounted for by the fact that the specimen of milk was obtained from a woman who had had extreme symptoms of one of the toxemias of pregnancy and also because of her small daily output of milk. Variations nearly as great, however, may occur between specimens from normal women in the same period of lactation. In searching for a possible cause for these extreme variations of chlorin content in human milk, the data have been studied from different points of view. The influence of the




Curves of maximum (upper curve), average (middle curve) and minimum (lower curve) amounts of chlorin in human milk.

period of lactation, of the volume of the secretion, of the time of collection during the day, of the ingestion of food and of psychic stimuli have been considered. As a basis for comparing the possible effects of these factors, it was thought advisable to establish, first, a normal figure. For this purpose, we have collected the results obtained on the milk of women whose environment, diet and temperament were most accurately known. These data were obtained largely from private patients living under most favorable circumstances and who were considered to be normal, physically and psychically, and who were giving an adequate amount of milk of such a quality that their babies developed normally for a period of at least six months.

The results obtained on the milk of these selected subjects are presented in Table 4.

TABLE 4.—Chlorin Content of Specimens from Normal Subjects (Lactating Types)

| Name | Number | Mg. Chlorin per 100 C.c. of Milk | | | Period of Lactation, Weeks | Approximate Amount of Milk in 24 Hours, C.c. |
|---|---|---|---|---|---|---|
| | | Before Nursing | After Nursing | Middle Nursing | | |
| Mrs. W. | 2 | 47.4 | .... | .... | 11 | 750 |
| Mrs. W. | 3 | .... | 39.3 | .... | .. | 750 |
| Mrs. T. | 25 | 25.9 | | | | |
| Mrs. T. | 26 | .... | 34.2 | .... | 2 | 750 |
| Mrs. H. | 13 | .... | .... | 36.0 | 3 | 600 |
| Mrs. H. | 88 | .... | .... | 32.0 | 10 | 750 |
| Mrs. S. | 16 | 37.2 | .... | .... | 3 | 660 |
| Mrs. St. | 45 | 50.0 | .... | .... | 7 | 720 |
| Mrs. St. | 46 | .... | 50.0 | | | |
| Mrs. St. | 149 | 48.0 | .... | .... | 11 | 450 |
| Mrs. St. | 150 | .... | 54.0 | .... | 11 | |
| Mrs. R. | 92 | .... | .... | 43.0 | 5 | 750 |
| Mrs. Ra. | 93 | .... | .... | 44.0 | 5 | 750 |
| Mrs. F. | 108 | .... | 49.4 | .... | 20 | 900 |
| Mrs. F. | 109 | .... | 45.3 | .... | 20 | 900 |
| Mrs. F. | 132 | .... | .... | 47.0 | 20 | 900 |
| Mrs. F. | 133 | 47.0 | .... | .... | 20 | 900 |
| Mrs. F. | 134 | 42.0 | .... | .... | 20 | 900 |
| Mrs. F. | 135 | 47.0 | .... | .... | 20 | 900 |
| Mrs. F. | 136 | 47.0 | .... | .... | 20 | 900 |
| Mrs. F. | 138 | 42.0 | .... | .... | 20 | 900 |
| Mrs. F. | 139 | 36.0 | .... | .... | 20 | 900 |
| Mrs. F. | 140 | 37.0 | .... | .... | 20 | 900 |
| Mrs. F. | 141 | 35.0 | .... | .... | 20 | 900 |
| Mrs. F. | 143 | 51.0 | .... | .... | 30 | 750 |
| Mrs. F. | 144 | .... | 51.0 | .... | 30 | 750 |
| Mrs. I. | 312 | 29.4 | .... | .... | 52 | 1,200 |
| Mrs. I. | 313 | .... | 30.0 | .... | 52 | 1,200 |
| Mrs. Str. | 298 | .... | .... | 30.0 | 5 | 750 |
| Mrs. Str. | 299 | .... | .... | 31.0 | 5 | 750 |
| Mrs. Str. | 300 | .... | .... | 32.0 | 5 | 750 |
| Mrs. Str. | 301 | .... | .... | 32.0 | 5 | 750 |
| Mrs. Str. | 302 | .... | .... | 32.0 | 5 | 750 |
| Mrs. Str | 303 | .... | .... | 30.0 | 5 | 750 |
| Mrs. Str. | 304 | .... | .... | 30.0 | 5 | 750 |
| Mrs. Wi. | 294 | .... | .... | 30.0 | 24 | 750 |
| Mrs. K. | 251 | 40.2 | .... | .... | 22 | 750 |
| Mrs. B. | 201 | 38.4 | .... | .... | 28 | 750 |
| Mrs. Kv. | 166 | 40.8 | .... | .... | 17 | 840 |
| Mrs. Q. | 125 | 42.0 | .... | .... | 3 | 750 |
| Mrs. Q. | 126 | 47.0 | .... | .... | 3 | 750 |
| Mrs. D. | 101 | 30.0 | .... | .... | 4 | 750 |
| Mrs. Sp. | 14 | 24.6 | .... | .... | 10 | 600 |
| Mrs. Sp. | 15 | .... | 28.2 | .... | 10 | 600 |
| Mrs. G. | 316 | 40.8 | .... | .... | 9 | 630 |
| Mrs. G. | 317 | .... | 36.0 | .... | 9 | 630 |
| Mrs. G. | 318 | 37.0 | .... | .... | 9 | 630 |
| Mrs. G. | 319 | .... | 35.0 | .... | 9 | 630 |
| Mrs. G. | 320 | 37.8 | .... | .... | 9 | 630 |
| Mrs. G. | 321 | .... | 37.8 | .... | 9 | 630 |
| Mrs. G. | 322 | 41.4 | .... | .... | 9 | 630 |
| Mrs. G. | 323 | .... | 38.4 | .... | 9 | 630 |
| Mrs. Sti. | 324 | .... | .... | 30.0 | 39 | 1,100 |
| Mrs. Sti. | 325 | .... | .... | 32.5 | | |
| Mrs. Sti. | 326 | .... | .... | 34.0 | | |
| Mrs. Sti. | 327 | .... | .... | 40.0 | | |

From the results presented in Table 4, it will be seen that the chlorin content of milk from so-called strictly normal subjects has a relatively narrow range of variation, after the first week of lactation, namely, from 30 to 50 mg. per 100 c.c. of milk (average 38.1 mg.). Attention should also be called to the fact that in these subjects little variation is noted in specimens taken before and after nursing and at

various periods during the day. The effect of the period of lactation on the amount of chlorin in human milk can be seen from the determinations recorded in Tables 3 and 4. Table 3, in which specimens from all types of patients are considered, shows that during the first two weeks of lactation there is a definite tendency for the chlorin content to be high, and that after this period no constant change takes place. Specimens with high and with low chlorin content will be found to occur at all stages of lactation. Table 4, on the other hand, shows that in "normal" subjects such variations do not occur during the first six

TABLE 5. — CHLORIN CONCENTRATION OF SPECIMENS OF HUMAN MILK FROM NORMAL WOMEN COLLECTED AT INTERVALS DURING THE DAY

| Number | Name | Time | Amount Collected, Oz. | Daily Amount, Oz. | Mg. Chlorin | Period of Lactation, Weeks |
|---|---|---|---|---|---|---|
| 210 | Mrs. L. | 6 a.m. | ... | 25¾ | 43.7 | 21 |
| 211 | Mrs. L. | 9 a.m. | ... | .... | 37.5 | 21 |
| 212 | Mrs. L. | 12 m. | ... | .... | 36.0 | 21 |
| 213 | Mrs. L. | 3 p.m. | ... | .... | 39.0 | 21 |
| 214 | Mrs. L. | 6 p.m. | ... | .... | 45.0 | 21 |
| 215 | Mrs. L. | 9 p.m. | ... | .... | 41.4 | 21 |
| 192 | Mrs. F. | 8 a.m. | 6¾ | .... | 15.0 | 26 |
| 193 | Mrs. F. | 8 p.m. | 6½ | 34½ | 19.5 | 26 |
| 186 | Mrs. A. | 6 a.m. | 3½ | .... | 32.0 | 17 |
| 187 | Mrs. A. | 9 a.m. | 4¾ | .... | 40.8 | 17 |
| 188 | Mrs. A. | 12 m. | 2 | .... | 32.0 | 17 |
| 189 | Mrs. A. | 3 p.m. | 2¾ | .... | 31.8 | 17 |
| 190 | Mrs. A. | 6 p.m. | 3 | .... | 31.8 | 17 |
| 191 | Mrs. A. | 3 p.m. | 2½ | .... | 32.0 | 17 |
| 170 | Mrs. W. | 6 a.m. | 5¾ | 35 | 28.8 | 22 |
| 171 | Mrs. W. | 9 a.m. | 8 | .... | 27.0 | 22 |
| 172 | Mrs. W. | 12 n. | 4¾ | .... | 24.0 | 22 |
| 173 | Mrs. W. | 3 p.m. | ... | .... | 26.8 | 22 |
| 174 | Mrs. W. | 6 p.m. | 5 | .... | 22.8 | 22 |
| 175 | Mrs. W. | 9 p.m. | ... | .... | 26.8 | 22 |
| 176 | Mrs. T. | 3 p.m. | ... | .... | 32.3 | 22 |
| 177 | Mrs. T. | 12 n. | ... | .... | 26.3 | 22 |
| 134 | Mrs. F. | 12 n. | ... | .... | 44.5 | 22 |
| 136 | Mrs. F. | 3 p.m. | ... | .... | 47.0 | 22 |
| 64 | Mrs. Q. | 12 m. | ... | 25 | 108.0 | 1 |
| 65 | Mrs. Q. | 3 p.m. | ... | .... | 108.0 | 1 |
| 66 | Mrs. Q. | 6 p.m. | ... | .... | 108.0 | 1 |
| 67 | Mrs. Q. | 10 p.m. | ... | .... | 108.0 | 1 |
| 68 | Mrs. Q. | 2 a.m. | ... | .... | 112.0 | 1 |
| 69 | Mrs. Q. | 6 a.m. | ... | .... | 117.0 | 1 |
| 70 | Mrs. Q. | 9 a.m. | ... | .... | 112.0 | 1 |
| 316 | Mrs. G. | 3 p.m. | ... | .... | 38.4 | 12 |
| 318 | Mrs. G. | 6 p.m. | ... | .... | 36.0 | 12 |
| 320 | Mrs. G. | 10 p.m. | ... | .... | 37.8 | 12 |
| 322 | Mrs. Q. | 6 a.m. | ... | .... | 39.9 | 12 |

months of lactation. From these observations we feel justified in concluding that after the first two weeks of milk secretion the concentration of chlorin in human milk is not related to the period of lactation. The effect of the volume of the milk and of the time of collection during the day on the concentration of the chlorids is shown in Table 5. The subjects represented in this table were wet nurses at the Boston Wet Nurse Directory, who were normal mothers giving relatively large amounts of milk. It will be noted that the average figure, as in the table of "normal" subjects, is about 40 mg., and that the chlorin concentration of the milk varies little in the specimens collected at three-

hour intervals during the day and bears no constant relation to the volume of milk obtained at three hour periods. There is, however, a tendency for somewhat higher figures to occur in the early morning and late evening specimens.

In Table 6 we have collected all the specimens of milk with the chlorin concentration above 50 mg. per 100 c.c. Although the subjects from whom these specimens were secured, were not known to us personally in all instances, they were mothers who were giving an amount of milk inadequate for the growth of the infant. From Tables 5 and 6 it will thus be seen, that after the supply of milk has been established, normal mothers, giving relatively large amounts of milk, always have between 30 and 50 mg. chlorin per 100 c.c. of milk, that this concentration does not vary constantly with the amount of milk obtained at three hour periods and that high chlorin concentrations tend to occur among mothers who for some reason cannot be regarded as "lactating types."

TABLE 6.—CHLORIN CONTENT OF SPECIMENS OF NORMAL SUBJECTS OF NONLACTATING TYPE

| Number | Name | Mg. Chlorin per 100 C.c. | Period of Lactation, Weeks | Daily Approximate Amount of Milk, C.c. |
|---|---|---|---|---|
| 295 | Mrs. S. | 82.0 | 4 | 210 |
| 308 | Mrs. S. | 69.0 | 6 | 180 |
| 309 | Mrs. S. | 60.0 | 6 | 180 |
| 289 | Mrs. P. | 114.0 | 22 | 300 |
| 290 | Mrs. P. | 102.0 | 22 | 300 |
| 291 | Mrs. P. | 98.0 | 22 | 300 |
| 257 | Mrs. S. | 90.6 | 5 | 200 |
| 258 | Mrs. S. | 114.0 | 5 | 200 |
| 227 | Mrs. W. | 67.0 | 48 | 15 oz. 450 |
| 168 | Mrs. H. | 75.0 | 3 | 15 oz. 450 |
| 169 | Mrs. H. | 87.0 | 3 | 15 oz. 400 |
| 197 | Mrs. H. | 77.7 | 5 | 12 oz. 360 |
| 117 | Mrs. S. | 96.0 | 13 | 10 oz. 350 |
| 59 | Mrs. P. | 112.0 | 15 | 250 |
| 248 | Mrs. P. | 51.6 | 24 | 120 |
| 249 | Mrs. P. | 52.8 | 24 | 120 |
| 54 | Mrs. P. | 86.0 | 4 | 15 oz. 400 |
| 89 | Mrs. W. | 59.0 | 4 | 10 oz. 300 |

The results presented in Table 5 indicate also that the chlorin content of milk is not influenced by the food as the values of milk chlorids in the first morning nursing, when no food had been taken since the evening of the previous day, were essentially the same as those obtained in the late afternoon and early evening, a time when one would expect the effects of ingested food to be apparent. It is, of course, conceivable that the chlorid content of milk might be altered by feeding diets poor or rich in sodium chlorid for relatively long periods, or by the administration of relatively large amounts of the same for short periods. For lack of suitable experimental material, it was impossible, unfortunately, to extend this line of inquiry in connection with our studies of human

milk. We have, however, carried out a considerable number of experiments dealing with this subject on goats and cows, the results of which work will be published at an early date.

TABLE 7.—CHLORIN CONTENT OF MILK FROM "UNSTABLE" SUBJECTS.

| Number | Name | Mg. Chlorin per 100 C.c. of Milk | | | Approximate Daily Amount of Milk, C.c. | Period of Lactation, Weeks |
|---|---|---|---|---|---|---|
| | | Middle Nursing | Before Nursing | After Nursing | | |
| 8 | Mrs. R. | .... | 25.0 | .... | 600 | 11 |
| 9 | Mrs. R. | .... | .... | 37.1 | 600 | 11 |
| 10 | Mrs. R. | .... | 32.0 | .... | 600 | 11 |
| 11 | Mrs. R. | .... | .... | 64.0 | 600 | 11 |
| 102 | Mrs. H. | .... | .... | 40.6 | 350 | 1 |
| 103 | Mrs. H. | .... | 76.5 | .... | 350 | 1 |
| 180 | Mrs. B. | 30.0 | | | | |
| 184 | Mrs. B. | .. . | 63.0 | .... | 600 | 3 |
| 185 | Mrs. B. | .... | .... | 60.0 | | |
| 198 | Mrs. S. | .... | 45.0 | .... | 600 | 13 |
| 199 | Mrs. S. | .... | .... | 102.7 | ... | 13 |
| 240 | Mrs. S. | 72.0 | .... | .... | ... | 17 |
| 241 | Mrs. S. | 66.0 | .... | .... | ... | 17 |
| 216 | Mrs. N. | .... | 40.0 | .... | 600 | 3 |
| 219 | Mrs. N. | 78.0 | .... | .... | 600 | 3 |
| 47 | Mrs. D. | .... | 90.0 | .... | 250 | 4 |
| 48 | Mrs. D. | .... | 57.0 | .... | 250 | 4 |
| 309 | Mrs. S. | .... | 41.4 | .... | 700 | 5 |
| 310 | Mrs. S. | .... | .... | 31.2 | 700 | 5 |
| 296 | Mrs. M. | .... | 48.0 | .... | ... | 2 |
| 297 | Mrs. M. | .... | .... | 72.0 | ... | 2 |
| 268 | Mrs. K. | 50.0 | .... | .... | ... | 2 |
| 269 | Mrs. C. | 50.0 | .... | .... | ... | 2 |
| | | 55.0 | .... | .... | 700 | 2 |
| 272 | Mrs. C. | 84.0 | .... | .... | 700 | 2 |
| 273 | Mrs. C. | 47.0 | .... | .... | 700 | 5 |
| 275 | Mrs. C. | 49.0 | .... | .... | 700 | 2 |
| 282 | Mrs. G. | 49.0 | .... | .. . | 700 | 5 |
| 283 | Mrs. G. | 49.0 | .... | .... | ... | 5 |
| 284 | Mrs. G. | 54.0 | .... | .... | ... | 5 |
| 285 | Mrs. G. | 59.0 | .... | .... | ... | 5 |
| 286 | Mrs. G. | 42.0 | .... | .... | ... | 5 |
| 264 | Mrs. I. | 36.0 | .... | .... | ... | 5 |
| 265 | Mrs. I. | 43.8 | .... | .... | ... | 3 |
| 266 | Mrs. I. | 49.8 | .... | .... | ... | 3 |
| 267 | Mrs. I. | 33.0 | .... | .... | ... | 3 |
| 221 | Mrs. N. | 72.0 | .... | .... | 600 | 3 |
| 205 | Mrs. N. | 49.8 | .... | .... | 600 | 2 |
| 216 | Mrs. N. | 40.0 | .... | .... | 600 | 3 |
| 217 | Mrs. N. | 43.8 | .... | .... | 600 | 3 |
| 218 | Mrs. N. | 42.0 | .... | .... | 600 | 3 |
| 219 | Mrs. N. | 78.0 | .... | .... | 600 | 3 |

In view of the well recognized effect of psychic stimuli on the composition of the urine and of the saliva, it seemed possible that this factor might be a cause for the variation in the concentration of chlorin in human milk. It was noted that in most instances the variations were found in specimens from women whose babies were growing unsatisfactorily, and who for this or other reasons may be classified as irritable or emotional mental types. In some instances, the daily volume of milk was sufficient for the baby but was subject to considerable variation. In Table 7 we have arranged the results of the analyses of specimens of milk from these so-called "unstable" types. It will be seen that in the milk of such mothers variations of as much as 100 per cent. occur in the chlorin content of specimens of milk obtained at different periods.

SUMMARY

A study of the chlorin content of 327 specimens of human milk has been made by the use of the McLean-Van Slyke titration method. It has been shown from these determinations that the average chlorin content of human milk from all types of mothers and at various stages of lactation is 38.1 mg. per 100 c.c. of milk. It has been noted that during the first two weeks of lactation, the chlorin content of human milk is somewhat higher. Specimens containing high and low chlorin concentration may be found in all stages of lactation. It has been found that the milk of strictly normal women giving a normal amount of milk has a relatively narrow range of variation in the chlorin concentration of their milk.

Observations on the relation of ingestion of food, of the time of collection of the specimens, of the volume of secretion and the effect of psychic stimuli, to the variation in the chlorin concentration of human milk have been made. It was found that in normal subjects the food intake and the time of day that the collection is made cause no outspoken change in the chlorin content of the milk. There is a slight tendency toward somewhat higher concentrations in specimens collected in the early morning and late evening. In women whose daily output is very large, there is an unmistakable tendency to the production of milk of a low chlorin content, and conversely those with a small amount of milk more frequently secrete milk containing a relatively high concentration of chlorids. This fact probably accounts for the statements in the literature to the effect that the concentration of the mineral constituents of the milk increase with each month of lactation, a finding which would, of course, go hand in hand with the decreased daily volumes usually noted in the later stages of milk production.

Our results would seem to indicate that the chlorin content of the milk can be affected markedly by psychic stimuli, as in phlegmatic mothers living under good conditions the chlorin content of the secretion remains constant from day to day and hour to hour. In the case of mentally unstable types, women also living under favorable conditions, large variations, frequently amounting to as much as 100 per cent., may occur. It has been noted that the babies with mothers of this type very frequently show evidences of intestinal indigestion and that as a rule the mothers are able to nurse their babies for relatively short periods.

CONCLUSIONS

1. The "salt" content of human milk is subject to great variations during all periods of lactation.

2. Estimation of the chlorin content of human milk can be obtained only by examining specimens from all nursings during the day.

3. The average chlorin concentration of milk from all types of women at all periods of lactation is 58.2 mg. per 100 c.c. of milk; the average after the second week of lactation is 52.6 mg.

4. "Normal" mothers, giving large amounts of milk, show a minimum variation in the chlorin concentration of their milk, with an average of 38.1 mg.

5. The greatest variation in the chlorin content of milk is found in specimens from "nervous" women.

6. Diet is not a cause for the variation in the chlorin concentration of human milk.

7. The chlorin concentration of milk from women, after the second week of lactation, who give large amounts of milk tends to be low and conversely the milk from women giving small amounts of milk is high in chlorin.

# INFANTILE SCURVY FOLLOWING THE USE OF RAW CERTIFIED MILK*

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From the fact that most textbooks on diseases of children state that scurvy may occur on a diet of raw milk, the extreme rarity of the occurrence is, perhaps, not sufficiently appreciated. The only direct references to such cases that I have been able to find are in the classic report of the American Pediatric Society [1] and in a paper by Dr. J. L. Morse.[2] The first of these authorities, under the heading "Food used at or shortly before scurvy developed," states: "Raw milk alone, 4; with breast milk and amylaceae, 1; total 5." No further details of the cases are furnished. The total number of cases in this report in which the character of the food is specified, is 356. Morse's report, embracing fifty-eight cases, includes one case on raw milk, but the length of time it had been administered and other details are not given. It is a curious fact that many more cases of scurvy are reported in infants fed on breast milk than on cow's milk feeding; in the American Pediatric Society report there are ten, and in Morse's report, three breast milk cases.

The case reported herewith is apparently the first in which raw milk had been given practically from birth, and it has the additional value in more clearly defining the issue, that certified milk exclusively was employed.

## REPORT OF CASE

*History.*—A girl, aged 10 months, was admitted to the Children's Clinic of Leland Stanford Junior University Medical School, Oct. 28, 1919. Complaint: "rheumatism." Father and mother are healthy, young American born people of Italian parentage, with no history or indicaton of syphilis or other disease. The patient is the first-born. There have been no previous pregnancies.

The baby was born at full term weighing 6 pounds, 7 ounces. She was never breast fed but from the first has been given on physician's advice a formula consisting of raw certified milk, Mead's dextrimaltose No. 1 and boiled water, with the addition to each bottle of the following preparation: Sodium citrate, 3 drams; distilled water, 2 ounces. Ten drops have been added to each feeding.

The formula was at first made up of one part of milk and two parts of water; at about 2 months it was changed to a half-and-half mixture, and at 9 months, to a two-thirds mixture. A teaspoonful of dextrimaltose was added to each bottle. Seven bottles a day, at three hour intervals, were given until the baby was 9 months old, since then three bottles a day have been given.

* Received for publication, Dec. 14, 1920.

* From the Subdivision of Pediatrics, Stanford University Medical School.

1. The American Pediatric Society's Collective Investigation on Infantile Scurvy in North America, Tr. Am. Pediat. Soc. **10**:5, 1898.

2. Morse, J. L.: Infantile Scorbutus, Boston M. & S. J. **170**:504, 1914.

The mother states that she has always offered the baby 8 ounces of the milk mixture and allowed her to take as much of it as she would. Until the present illness began the baby made, apparently, satisfactory progress in weight and growth. Shortly after the symptoms began, the diet was changed so that the infant received three bottles a day supplemented by farina, eggs, Italian pastes with a little olive oil, but no fresh vegetables, fruit or fruit juices have ever been given. Except for two days, when the baby was 6 months old, nothing but certified milk has been used. The mother was very emphatic on this point and brought a bottle of the milk to corroborate—as it did—her assertion. The formula has never been boiled or heated, except when it was warmed at feeding time. From the feeding history it would appear that the physician in giving the mother his instructions had kept in mind the dangers of scurvy from heated milk.

*Present Illness.*—The first symptoms were noticed by the mother about July 1, when the baby was 6 months old. In putting on the baby's stockings, the mother noticed that the left tibia was tender, and about a month later the baby cried when the shoes were put on. The tenderness increased slowly. About a month ago (toward the end of September) swelling and pain in the knees were noticed, and a week later the mother found one morning that the mouth was bloody. On investigation she saw that the blood was coming from the gums.

Questioned as to trauma, the mother stated that in August, when the child was lifted from a chair the left foot caught in one of the rungs and the baby cried for a moment. In September, the baby had "fever" for three days, and since then has seemed to be "sore all over," but suffers most when the napkins are changed or stockings are put on. A diagnosis of "rheumatism" was made by the physician, but the mother was not satisfied with this diagnosis.

*Physical Examination.*—The baby is pale and pasty looking and very irritable when handled. The face is full, but the body is not well padded. The legs are flexed with the thighs everted and are held motionless. There is no craniotabes nor bossing. There is slight seborrhea of the scalp. Seven teeth are fully erupted. The gums around all these, but especially around the upper incisors, are swollen, purplish in color and bleed readily when touched. There is slight beading of the ribs, and a shallow Harrison's groove. The abdomen is not protuberant. Heart and lungs are normal. The liver is palpable about 2 cm. below the costal margin. The spleen is not palpable. The genitalia are somewhat inflamed. On the buttocks are a number of small nearly healed excoriations. The lymph nodes are not enlarged. The wrist epiphyses are moderately enlarged but not tender. The lower femoral epiphyses are much enlarged, and the soft tissues over them are thickened. The knees are acutely tender, and motion is evidently very painful. The ankles and lower tibiae are also somewhat swollen and tender to pressure. About the right malleolus there is a faint bluish discoloration suggestive of a deep ecchymosis.

Impression: Scurvy and slight rickets.

*Laboratory Examination.*—Nov. 3, 1919: Erythrocytes, 4,219,000; hemoglobin 75 per cent.; leukocytes, 12,300; polymorphonuclears, 55 per cent.; lymphocytes, 40 per cent.; large mononuclears, 3 per cent.; transitionals, 2 per cent. The red blood cells were normal in shape, size and coloring. No normoblasts, megaloblasts or malarial parasites were seen.

November 4: Wassermann negative.

*Roentgen-Ray Examinations.*—Oct. 31, 1919: "Examination shows thickening along the diaphysis sides of the epiphyseal lines of all the long bones of the legs and forearms; slight periostitis about the upper part of the right tibia; apparently slight posterior displacement of the epiphyses of both femora."

November 4: "Further examination of both knees shows evidence of posterior displacement of the epiphyses of both femora; thickening along the diaphysis side of the epiphyseal line, as previously reported."

November 15: "Examination of both legs, for comparison, shows evidence of thickening along the diaphysis side of the epiphyseal lines of all the long bones; considerable periostitis along the shafts of the long bones."

November 25: "Examination of both legs, for comparison, shows decrease in the thickening about the epiphyseal lines; periostitis about the same as at last examination."

*Treatment.*—The child was put on a top milk mixture with additions to the diet of cooked cereals, vegetable purees, yolk of egg, baked potato and 4 ounces of orange juice daily. No medication was given.

*Later Progress.*—The improvement was so rapid that the child was discharged in nine days (November 6) from the hospital with instructions to the mother to bring the child to the clinic. In spite of the posterior displacement of the lower epiphyses of both femurs, the baby was moving both legs voluntarily by November 4. The general appearance was greatly improved. The gums had resumed their normal color. The legs were still considerably enlarged at knee and ankle but were only slightly tender. Orange juice, 2 ounces a day, was continued. The child when last seen in the clinic, December 6, was practically normal in appearance and had gained about a pound and a half in the month since her discharge from the hospital.

## COMMENT

Clinically, this case was typical scurvy. The diagnosis was fully corroborated by roentgenogram and by the prompt and complete disappearance of symptoms without medication on a diet rich in antiscorbutic substances. Mild rickets was also undoubtedly present.

The principal interest of this case lies in the clear and complete dietary history extending from birth to the time of the patient's discharge from the clinic. The parents were intelligent and apparently sure of their facts. That raw certified milk had been used continuously seems to be beyond question. The undoubted extreme rarity of scurvy in infants fed on raw cow's milk demands a discussion of the possible causes of scurvy in this infant.

Two explanations may be advanced, first, that the amount of milk taken was too small; second, that the antiscorbutic vitamin was partly or wholly destroyed by some other agent than heat.

The experimental work of Chick, Hume and Skelton [3] explained certain discrepancies in the conclusions of previous investigations on the antiscorbutic vitamin content of raw cow's milk by showing that while this vitamin is present in cow's milk, its concentration is low. Guinea-pigs receiving less than 50 c.c. of cow's milk a day invariably developed scurvy. This observation has been confirmed by several workers. In a recent investigation [4] I found a somewhat higher concentration in raw milk produced near San Francisco but noted the invariable appearance of scurvy when less than 30 c.c. was fed. The

3. Chick, H.; Hume, E. M., and Skelton, R. F.: The Antiscorbutic Value of Cow's Milk, Biochem. J. **12**:131, 1918.

4. Faber, H. K.: Sodium Citrate and Scurvy, Proc. Soc. Exper. Biol. & Med. **17**:140, 1920.

experimental evidence, therefore, goes to show that the occurrence of scurvy in man might be due to too low an intake of raw milk, as well as to the use of milk in which the vitamin had been destroyed by heat or by other agents.

In the present case, a dilute formula (1 part milk, 2 parts water) was used up to the age of 2 months, and thereafter the strength was only 1 part milk and 1 part water. The exact quantities taken daily are not known, but the mother stated that the baby, except when very young, usually finished a bottle of 8 ounces every three hours, a total of seven bottles daily. It appears likely, therefore, that between the ages of 2 and 9 months, the period during which scurvy developed, the baby must have taken an average of nearly 28 ounces of milk daily. Since an intake of this amount is not often exceeded by infants between the ages stated, and since scurvy so rarely occurs during feeding with raw milk, it seems unlikely, though perhaps not impossible, that a quantitative deficiency could have been responsible for the occurrence of scurvy in the present case.

The second possibility—that the antiscorbutic vitamin had been destroyed—remains to be considered. Aging of the milk can hardly be thought of, since the vigilant milk commission of the San Francisco County Medical Society demands prompt marketing of all milk which it certifies. The possibility that the sodium citrate, added to each bottle taken by the patient since the first week of life, may have had a deleterious effect on the antiscorbutic vitamin deserves consideration.

Alkalization has been proposed by Hess and Unger [5] as one of the causes of destruction of vitamin. They state that even such small quantities of alkali as are contained in certain infant foods may be sufficient to destroy the antiscorbutic vitamin in milk.[6]

A determination of the effect of sodium citrate on the hydrogen-ion concentration of a sample of raw milk, done through the kindness of Dr. E. C. Dickson, showed that an addition to the amount of 0.25 per cent. lowered the $P_H$ from 6.45 to 6.50; of 0.5 per cent., to 6.95; and of 1 per cent., to 7.05. The addition of 10 drops of an 18 per cent. solution of sodium citrate to 8 ounces of whole milk—the approximate amounts in the present case—giving a strength of 0.05 per cent., would lower the acidity by considerably less than $P_H$ 0.05; probably, as shown by the plotted curve, by less than $P_H$ 0.01. Such an alteration of acidity should be regarded as probably insignificant.

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5. Hess, A. F., and Unger, L. J.: The Deleterious Effect of the Alkalization of Infant's Food, J. A. M. A. **73**:1353 (Nov. 1) 1919.

6. It is only fair to state that this assertion has been disputed by several competent clinicians. (See discussion following Hess and Unger's report.) Mead's dextri-maltose No. 1 is stated by the manufacturers to contain 2 per cent. added sodium chlorid, but it apparently contains no added alkali.

In a series of experiments [4] it was shown that additions of from 0.25 to 2 per cent. of sodium citrate to raw milk apparently reduced the antiscorbutic vitamin content, since in eight out of nine guinea-pigs fed on citrated milk, scurvy developed, while in the control series of eight animals, fed on raw milk alone, scurvy developed in only two, both of which took an average of less than 34 c.c. of milk daily. None of the animals in the citrate series took less than 35 c.c. daily and the average of the citrate series was 41.8 c.c. as compared with an average of 40.7 c.c. for the controls. It should, however, be pointed out that none of the experimental animals received as little sodium citrate as was given to the human case here reported. In the latter the concentration of sodium citrate in the formula was approximately 0.05 per cent., or a total of about 0.84 gm. daily. The long period of continuous administration may, however, be considered. Knowing that the concentration of vitamins in cow's milk is low, that the concentration was reduced to one third for the first two months and to one half during the next seven months, may not the amount of added citrate have been sufficient to lower the vitamin concentration just below the scorbutic threshold?

Assuming this to have been the case, I do not feel that we have as yet sufficient evidence to attempt an analysis of the modus operandi of sodium citrate in injuring the antiscorbutic vitamin. The degree of alkalization it produced in the patient's food was probably negligible. Bosworth and Van Slyke's [7] observation that sodium citrate forms in milk a soluble sodium paracaseinate would not appear relevant to the question of scurvy. Certainly, the citrate ion—present in large amounts in so many antiscorbutic foods—cannot be brought into discussion. Finally, in spite of the presence of a certain amount of positive evidence and in the absence of other apparent antiscorbutic factors, it is not certain that in the present case sodium citrate was actually at fault. It would, however, appear justifiable to regard sodium citrate in formula preparation with considerable distrust and to give preference to other substances, such as barley water, over the mineral salts when we wish to alter the coagulability of cow's milk.

## SUMMARY

1. An infant fed almost from birth on modified raw certified milk, to which small amounts of sodium citrate were added, developed scurvy at the age of 6 months.

2. It is possible, but not proved, that sodium citrate may have partly destroyed the antiscorbutic vitamin.

3. The use of sodium citrate in infant feeding over long periods should be provisionally regarded as dangerous.

7. Bosworth, A. W., and Van Slyke, L. L.: Why Sodium Citrate Prevents Curdling of Milk by Rennin, Am. J. Dis. Child. **7**:298 (March) 1914.

# INDICANURIA IN THE NEW-BORN *

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This study was undertaken for the purpose of observing the reaction for indican in the urine of the new-born under physiologic conditions

Momidlowski [1] tested for indican in the urine of three healthy infants between the ages of 10 and 12 days. He obtained intense reactions which on the second and third day following were negative or showed only traces.

Von Reuss [2] found indican in the urine in breast fed children during the first nine days of life rather frequently, often without the observation of any clinical symptoms. He states that it occurs in the well nourished, in the undernourished, in the constipated, and in diarrheic infants alike. Indican was not obtained on the first day and rarely on the second. It was most frequently found on the third and fourth days, but was found during the days following. As possible causes of this indicanuria, the absorption of indol from the intestinal content must be considered and also the parenteral formation of indican, which may be taken as a sign of tissue destruction. Von Ruess brings out the disproportion between the intensity of the indicanuria and the putrefactive manifestations in the stool. The fact that Hecht was unable to recognize indol in the meconium suggests that indican may result from the breaking down of tissue protein.

Maccone,[3] in a large series, records only one case in which the urine of the new-born was examined for indican and in this instance it was absent.

*Technic.*—The cases taken for study were from the nursery ward of the hospital. The urine of all infants delivered was examined. No cases were picked. The infants all were normal newly-born infants. The urines were examined during two different periods one month apart. No change in the routine care of the infants was made, except that daily specimens were collected by means of test tubes or Spicer's urinals. An unsuccessful attempt was made to examine single

* Received for publication, Nov. 3, 1920.
* From the Maternity Ward of the Presbyterian Hospital.
1. Jahrb. f. Kinderheilk. **26**:199, 1893.
2. Ztschr. f. Kinderheilk. **111**:12, 1911.
3. Riv. di clin. Pediat. **27**:1, 1919.

specimens of morning urine from each infant every day for fifteen days. A complete urine examination was made whenever a positive indican reaction was found. All such examinations failed to reveal any pathologic findings. All urines were examined within a few hours after collection.

The tests were made with Obermayer's reagent, which was made up of strong hydrochloric acid of 1.19 specific gravity, to which had been added two parts to the thousand of ferric chlorid. The urine was precipitated with a weak solution of lead acetate and filtered through filter paper. Fifteen c.c. of the filtered urine were mixed with 15 c.c. of Obermayer's reagent, and 2 c.c. of chloroform were added. The tube was then slowly inverted several times to mix thoroughly and allowed to stand for five minutes before reading. No coloration or a very faint blue was considered a negative reaction (0). A definite but faint blue was regarded as a trace, (±); an undoubted blue was regarded as a one plus (+) reaction; a deep blue as a two plus (++) reaction, and a very deep blue as a three plus (+++) reaction. The results obtained are shown in the accompanying table.

Out of 338 specimens of urine tested, twenty-eight, or 8.2 per cent., showed positive indican reactions. In five cases a positive reaction was obtained more than once. The reactions occurred most frequently and were more intense on the third, fourth and fifth days. No reactions were obtained on the eighth, ninth, eleventh, twelfth and fifteenth days.

Of significance is the fact that indicanuria most frequently is obtained during that period of life when the transitory fever of the new-born, and the transition from meconium to milk stools occurs when the weight has reached the lowest point.

There are probably two sources from which indican is derived. The first is decomposition of tissue protein and the second is putrefaction of protein in the bowel. That destruction of tissue protein to a considerable extent occurs during the first few days of life and particularly during the first five or six days of life is no doubt true. There are several factors which seem to speak for this. An initial loss of weight is common during the first five days, a larger portion of which is due to loss of body fluids but evidently some destruction of tissue protein takes place during this period when the infant receives insufficient nourishment. The presence of a relatively high amount of uric acid in the urine of the new-born and the frequent finding of uric acid infarcts in the kidneys at autopsy brings forth further evidence of possible destruction of tissue protein. Nitrogen deficiency in the early days of life has been observed by some investigators. This finding would speak strongly for tissue destruction. However, such a deficiency has not been established with certainty as yet.

It has been found by Blumenthal [4] and Rosenfeld that a small quantity of indican is probably formed in the adult during fever. Scholz,[5] however, could not find an increase in indican due to breaking down of tissue protein.

TABULATION OF RESULTS

| Case Number | Day | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| 1 | — | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — |
| 2 | — | — | 0 | — | — | — | — | 0 | 0 | 0 | — | — | — | — | — | — |
| 3 | — | — | — | 0 | 0 | 0 | 0 | — | 0 | — | — | — | — | — | — | — |
| 4 | — | 0 | 0 | 0 | — | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — |
| 5 | — | — | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — |
| 6 | — | — | 0 | 0 | ± | 0 | 0 | 0 | — | 0 | — | — | — | — | — | — |
| 7 | — | 0 | 0 | — | 0 | 0 | 0 | — | — | — | — | — | — | — | — | — |
| 8 | — | — | 0 | 0 | — | — | — | 0 | 0 | 0 | — | — | — | — | — | — |
| 9 | — | 0 | 0 | ± | — | — | 0 | 0 | 0 | 0 | — | — | — | — | — | — |
| 10 | — | +++ | ± | + | 0 | — | 0 | 0 | — | 0 | — | — | — | — | — | — |
| 11 | — | — | 0 | ++ | ± | ± | — | 0 | 0 | — | — | — | — | — | — | — |
| 12 | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — |
| 13 | — | — | 0 | 0 | — | — | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — |
| 14 | — | — | — | + | — | — | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — |
| 15 | — | — | +++ | 0 | 0 | 0 | 0 | — | — | — | — | — | — | — | — | — |
| 16 | — | — | — | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — |
| 17 | — | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — |
| 18 | ± | — | — | — | 0 | 0 | 0 | — | 0 | — | — | — | — | — | — | — |
| 19 | — | — | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ± | 0 | — |
| 20 | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | — | — | — | — | — | — |
| 21 | — | — | 0 | ± | 0 | 0 | 0 | — | 0 | ± | — | — | — | — | — | — |
| 22 | — | — | 0 | 0 | 0 | ± | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — |
| 23 | — | 0 | — | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — |
| 24 | — | — | — | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — |
| 25 | — | — | 0 | — | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — |
| 26 | — | 0 | — | 0 | 0 | 0 | 0 | — | 0 | — | + | — | — | — | — | — |
| 27 | — | 0 | 0 | 0 | 0 | 0 | — | 0 | 0 | 0 | 0 | — | — | — | — | — |
| 28 | — | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | — | 0 | — | — | — | — | — |
| 29 | — | — | 0 | 0 | 0 | — | 0 | 0 | 0 | 0 | — | — | — | — | — | — |
| 30 | — | — | 0 | 0 | 0 | + | — | 0 | 0 | 0 | — | — | — | — | — | — |
| 31 | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — | — |
| 32 | — | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — |
| 33 | — | — | 0 | 0 | 0 | 0 | ± | 0 | — | — | — | — | — | — | — | — |
| 34 | 0 | 0 | 0 | — | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — | — |
| 35 | — | — | — | — | + | 0 | — | 0 | 0 | — | — | — | — | — | — | — |
| 36 | 0 | 0 | +++ | + | — | — | — | — | 0 | 0 | 0 | — | — | — | — | — |
| 37 | — | — | 0 | 0 | 0 | 0 | — | — | 0 | 0 | 0 | — | — | — | — | — |
| 38 | — | — | — | — | — | — | — | — | 0 | — | — | — | — | — | — | — |
| 39 | — | — | 0 | 0 | 0 | 0 | — | 0 | 0 | — | — | — | — | — | — | — |
| 40 | — | — | — | — | — | — | 0 | — | 0 | — | — | — | — | — | — | — |
| 41 | — | — | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — |
| 42 | — | — | 0 | 0 | 0 | 0 | 0 | — | 0 | 0 | — | — | — | — | — | — |
| 43 | — | — | — | — | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — | — |
| 44 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — |
| 45 | — | — | — | 0 | 0 | 0 | 0 | 0 | 0 | — | — | — | — | — | — | — |
| 46 | 0 | 0 | — | — | +++ | 0 | 0 | 0 | 0 | — | — | — | — | — | — | — |
| 47 | — | 0 | — | 0 | 0 | 0 | 0 | — | — | — | — | — | — | — | — | — |
| 48 | — | — | — | +++ | 0 | — | — | — | — | — | — | — | — | — | — | — |
| 49 | — | 0 | — | — | +++ | 0 | 0 | — | 0 | 0 | 0 | 0 | — | — | — | — |
| 50 | — | 0 | + | 0 | 0 | 0 | — | — | — | — | — | — | — | — | — | — |
| Total.. | 5 | 19 | 32 | 36 | 41 | 37 | 38 | 34 | 40 | 30 | 15 | 6 | 2 | 2 | 1 | 0 |
| Positive... | 1 | 1 | 5 | 8 | 5 | 3 | 1 | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 0 | 0 |
| Negative.. | 4 | 18 | 27 | 28 | 36 | 34 | 37 | 34 | 40 | 28 | 14 | 6 | 2 | 1 | 1 | 0 |

The total number of specimens examined was 338.

It was noticed in this series of cases that there was no apparent connection between the amount of weight lost and the frequency of a positive indican reaction. Likewise, no relationship between the transitory fever of the new-born and indicanuria could be established.

4. Charité Annalen, **27**:46, 1903.
5. Ztschr. f. phys. chemie **38**:513, 1903.

Although it is fairly evident that there is destruction of tissue protein during the early days of life it is hard to say whether some of the indican is formed by this method. The fact that a positive reaction was obtained on the first and second days would speak for a parenteral formation of indican. These results, however, cannot be considered as absolute proof of such a fact as it is impossible to rule out intestinal putrefactive processes at such an early date.

Decomposition of protein in the bowel is usually considered the chief source of indican in the urine. The finding of indicanuria in the new-born suggests two possibilities other than parenteral formation: increased absorptive action of the bowel, and increased putrefaction in the bowel. Von Ruess speaks of the disproportion between the putrefactive manifestations in the bowel and the intensity of the indican reaction. It is known that the bowel in its entire length contains bacteria within twenty-four hours after birth. The possibility of putrefaction of the intestinal contents is therefore apparent. The meconium at first is sterile, due probably to a lack of moisture. Introduction of fluids into the gastro-intestinal tract with consequent increase of gastric and intestinal juices might supply the moisture necessary to render the meconium an ideal medium for the growth of putrefactive bacteria and the formation of putrefactive substances. The transition of meconium to the milk stool is a gradual process taking several days. Thus it may be possible that during this transition to the milk stool of fermentative type of stool there is an increased amount of putrefaction in the bowel.

As regards an increased absorptive action of the bowel, the findings of Grulee and myself,[6] published in a recent paper, may have some bearing. It was found that during the first few days of life the intestines were frequently permeable to a foreign protein, egg-white, as shown by positive precipitin reactions in the urine. While these findings can only be interpreted as specific for the protein tested, it appears possible that in the intestine of the new-born there may be an increased absorption of not only egg-white but of other substances, such as indol.

## SUMMARY

Indicanuria in the new-born occurred in twenty-eight, or 8.2 per cent., of 338 examinations, and in twenty cases of fifty examined.

Indicanuria, in all probability, may be considered physiologic, as it could not be associated with any pathologic findings clinically.

I wish to express my gratitude to Dr. Clifford G. Grulee for his many suggestions.

6. Am. J. Dis. Child., in press.

# CLINICAL DEPARTMENT

## POSTOPERATIVE RECURRENCE OF INTUSSUSCEPTION *

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To meet a case of intussusception in a patient who has been operated on previously for the same condition has been considered an infrequent occurrence. The following cases of postoperative recurrence of intussusception seen within a very short time at Lebanon Hospital, New York, have, because of the supposed rarity of the condition, prompted me to record them and to investigate the literature on the question.

### REPORT OF CASES

I saw Cases 2 and 3 during both illnesses, Case 1 during the second illness, and Case 4 during the first attack.

CASE 1.—Arnold Z., aged 6 months, was brought to Lebanon Hospital, Aug. 23, 1917, having shown signs and symptoms of acute intussusception for the preceding six hours. A laparotomy was performed immediately by Dr. Bookman, who reduced a large ileocecal intussusception and the child made a rapid recovery. An appendectomy was performed at the same time. June 6, 1918, about ten months later, the child was seized with a second attack of intussusception, was brought to Lebanon Hospital after four hours, when Dr. M. S. Kakels reduced an ileocecal intussusception. The child made an uneventful recovery and was discharged cured.

CASE 2.—Isidore G., aged 7½ months, was brought to Lebanon Hospital, March 17, 1919, almost in a state of extremis suffering from an acute intussusception of less than twenty-four hours' duration. The child was operated on at once by the house surgeon. An ileocecal intussusception was completely reduced without any difficulty. During a period of about thirty hours the child did very well. It recovered from its shock, it had normal bowel movements, was very playful and to all intents and purposes was on the high road to complete recovery. However, after about thirty hours, the child again began to cry as if in severe pain, it again passed blood stained mucus, a mass could be felt in the abdomen and for a second time the child went into a condition of severe shock. The child was again operated on by Dr. M. S. Kakels who reduced another intussusception of the same type. A second attack so severe and within so short a period after the first was too great for the child to bear and it died soon after the operation.

The following case deserves lengthy description not alone because of the rarity of the condition, but also because of the atypical symptoms occurring during the second attack.

* Received for publication, Dec. 6, 1920.

CASE 3.—Evelyn J., 10 months old, was born of apparently healthy parents, had a normal birth and development, was breast fed up to 8 months and was then placed on artificial feedings.[1] At the age of 6 months, the child was suddenly taken ill with an acute attack of intussusception of which the symptoms were unmistakable and well defined. The child was in shock, a well defined tumor could be felt in the abdomen and two diapers were stained with blood and mucus. Enemas were ineffectual. The child came to operation about four hours after the onset of symptoms, and Dr. L. M. Kahn reduced an ileocecal intussusception. The child made a very rapid recovery.

Nov. 6, 1919, about 3 a. m., four months after the first operation, the child was suddenly seized with repeated attacks of cramps at intervals of from ten to fifteen minutes. The attacks lasted up to about noon of the same day. An enema given that morning was returned with a very small amount of yellowish-brown fluid feces, some mucus but no blood. The last normal stool was passed in the morning of the preceding day. The child did not vomit.

I saw the patient for the first time at 3 p. m. The child looked perfectly well, was very playful, did not cry and its cheeks appeared to be of good color. The temperature per rectum was 100.4 F.; the pulse, 120. A complete physical examination was made and all findings were negative, except the abdominal signs. On gentle palpation the right side of the abdomen was found to be rigid and was apparently tender as the child would cry out and make attempts to push away the examiner's hand. The child did not react in the same way when the left side was manipulated. No masses could be felt in the abdomen or rectum and the finger withdrawn from the rectum showed no signs of blood or mucus. The signs at this time, indicative of an intra-abdominal surgical condition, were rigidity and tenderness, and, although the possibility of the presence of an intussusception suggested itself to me, I did not feel justified in making that diagnosis as I felt that I did not have sufficient evidence, especially after the child had been operated on previously for that condition. I left the patient with orders that nothing be given by mouth, that an enema be given with a rectal tube, and the returns noted for blood and mucus.

At 6 p. m. I was called again, and although the child's general condition was very good, she still showed the localized rigidity and tenderness on the right side of the abdomen. At this time also no masses could be felt in the abdomen; rectal examination was again negative, and there were no attacks of cramps during that afternoon. The temperature was normal, and the pulse was 124. One additional sign appeared at this examination and that was a very scant fecal movement with blood stained mucus following an enema.

My earlier suspicion that the child was suffering from a subacute attack of intussusception was now somewhat confirmed, but was made very doubtful by the absence of a palpable tumor in the abdomen or per rectum, by the absence of vomiting, and by the good general condition of the child. Another enema was given and the returns were again as last described.

The absence of diarrhea and rise in temperature made an ileocolitis very questionable. The rigidity and tenderness together with a history of cramps made it important to eliminate appendicitis, but the additional signs of blood stained mucus on two diapers, together with definite constipation, in spite of the important negative symptoms, suggested a recurrent intussusception so strongly that I felt a laparotomy was indicated.

The child was sent to Lebanon Hospital and Dr. Bookman reduced a very small ileocecal intussusception without any difficulty. An appendectomy was also performed. Up to the present, about ten months after the last attack, the child has been gaining weight and is in very good condition.

Dr. Henry Roth has brought to my attention another interesting case that I record with his kind permission.

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1. Reported before Society of Alumni of Lebanon Hospital, Jan. 6, 1920.

CASE 4.—Gertrude L., aged 10½ months, was admitted to Dr. Henry Roth's private service, Jan. 30, 1919, suffering from an acute intussusception. Dr. Roth operated, and on opening the abdomen found that spontaneous reduction had already occurred, and at the site of the intussusception, which was confined to the ileum, there was a section of the bowel that was congested and edematous. The appendix was removed.

March 18, 1920, the child was again admitted to Lebanon Hospital suffering from another intussusception. At intervals, between the first and second attack, the patient had transient attacks of cramps and bloody stools. For a number of hours prior to admission, the child suffered from cramps, had vomited repeatedly and had passed blood stained mucus. A second operation, performed by Dr. Henry Roth, revealed an ileo-ileal intussusception involving the same portion of bowel as in the first instance. Reduction was not difficult, and the child was again discharged as cured.

Looking back over a series of forty-one cases of intussusception, treated at Lebanon Hospital during about eight years, the four cases mentioned above were the only ones in which postoperative recurrences were present, and these at intervals of ten months, thirty hours, four months and fourteen months, respectively. Fourteen of these forty-one patients died, and one patient left the hospital, the parents having refused to allow the child to remain for operation, thus leaving twenty-six patients discharged as cured. Of these, four had second attacks for which they were operated on again.

I have collected seventeen cases from the literature in which a total of thirty-six operations were performed for the reduction of intussusception. Added to the four cases reported in this paper we have a total of twenty-one patients who were operated on forty-four times. Two patients had three operations each. One patient who had had five attacks was operated on twice. The longest interval between operations was three years; the shortest thirty hours.

Kellock reports a most remarkable case of recurrent intussusception in a child who had five attacks with final recovery, operations having been performed to relieve the third and fifth attacks. Nonsurgical procedures, such as enemas and air inflation, reduced the others.

Mahon [3] reports one case of postoperative recurrence of intussusception three years after the first operation, and reviews six other cases that he had found in the literature. These six cases included two of Clubbe, occurring two and six months after the first operation, in a series of 144 cases; one case in a series of 100 cases reported by Adams and Cassidy; one case of Gould, in which two operations were performed on the same patient at an interval of one month; one case reported by C. N. Dowd, in which recurrence took place three and one-half months after first operation, and another case of Cleveland with recurrence after five weeks.

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2. Lancet, **2**:154, 1912.
3. Guys Hosp. Gaz. **27**:356, 1913.

Turner [4] reports a case in which operation was performed three times, the third operation occurring nearly one year after the first attack. At the third laparotomy eighteen inches of ileum marked by tuberculous ulcers were resected, a lateral anastomosis was performed and the patient recovered. The same author records a case that showed unquestionable signs of intussusception three months after an operation for the same condition, but on entering the abdomen a second time, no intussusception was found. Spontaneous reduction probably occurred during anesthesia, as in the case of Dr. Roth. I have encountered one or two similar instances in which after an undoubted diagnosis of intussusception was made, laparotomy did not reveal the condition and in which, in all probability, spontaneous reduction had taken place during the administration of the anesthetic.

Eccles and Laidlaw,[4] in a series of 89 cases, report the case of one patient admitted on two separate occasions at an interval of three months. The patient recovered after two operations for ileocecal intussusception.

Allen,[6] in a review of twenty-seven cases of intussusception extending over a period of seventeen years, reports one case operated twice within four days at the Children's Hospital, Philadelphia.

Peskind [7] reports a case of intussusception in an infant, followed by obstruction of the bowels three weeks later and a second operation for intussusception.

Hipsley,[8] in a résumé of fifty-one cases of intussusception, mentions two cases of recurrence, one in which operation was done three times within a period of ten weeks, with final recovery, and a second case with recurrence after three months. He also refers to a case in the series, but of which he had no record, where recurrence took place four months after the first operation.

Graham [9] reports a case occurring in a boy, age 14 years, operated on for ileocecal intussusception May 30, 1916, and again July 11, 1916, when an irreducible intussusception was found. At the second operation four inches of the ileum were excised. Sections of the excised bowel showed the presence of small round celled sarcoma.

## CONCLUSIONS

1. Repeated attacks of intussusception in individuals previously operated on for the same condition, although very unusual, are not as infrequent as we might have believed they were.

4. Lancet **1**:169, 1914.
5. St. Barth. Hosp. Rept. **47**:97, 1912.
6. Ann. Surg. **59**:258, 1914.
7. Am. J. Dis. Child. **14**:63 (July) 1917.
8. Med. J. Australia **2**:383 (Nov. 9) 1918.
9. Brit. M. J. **2**:801, 1916.

2. In the event of an acute abdominal condition in a child previously operated on for intussusception, we must not neglect to give serious consideration to a probable recurrence.

3. That most of these cases of intussusception are of the ileocecal type suggests very strongly some anatomic factor as a probable predisposing cause and that some operative procedure, if possible, ought to be established to prevent recurrence.

I am indebted to the visiting surgical staff of Lebanon Hospital for permission to report hospital cases.

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